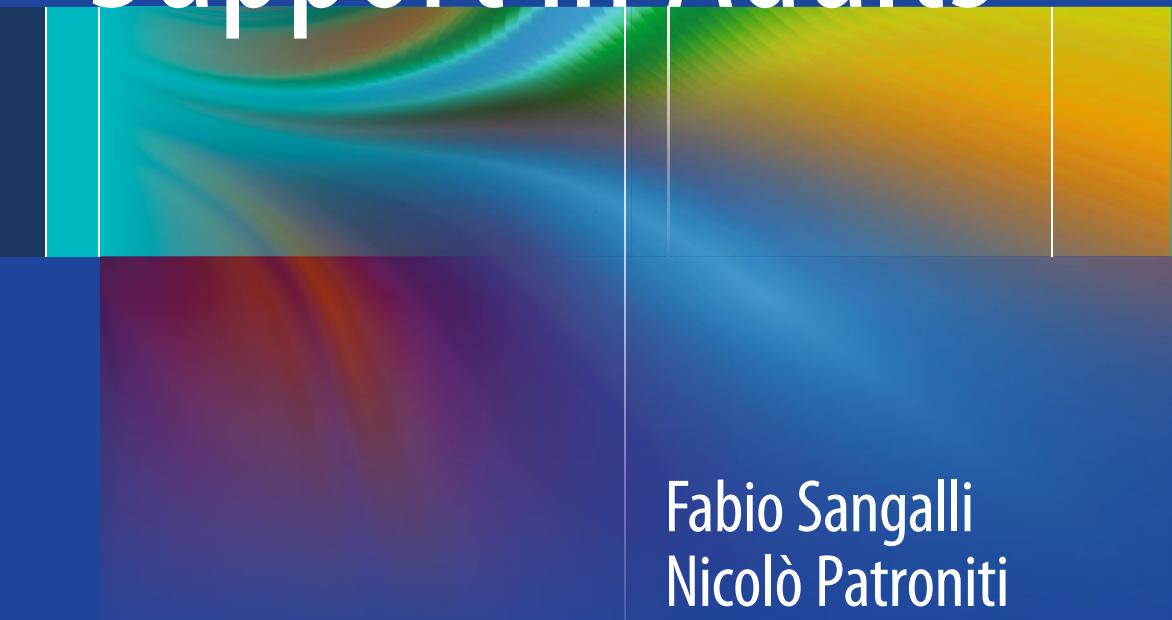


ECMO- Extracorporeal Life Support in Adults



Fabio Sangalli
Nicolò Patroniti
Antonio Pesenti
Editors



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Springer

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Foreword

The best way to temporarily support or substitute vital organs is based on the availability of reliable and effective tools able to vicariate the failing natural organ. This opportunity was achieved long ago for the kidney and, later on, for the heart and lung. The technological improvement that miniaturized the apparatus improved the vascular access, increased the performance of the artificial support, and has allowed to expand the use of circulatory and respiratory extracorporeal support to several clinical situations and to different ICUs (cardiac, respiratory, general). The advent of new fulminant diseases (H1N1 respiratory failure) and the improvement of out-of-hospital care for cardiac arrest are two situations that recently have seen extracorporeal support as a possible life-saving application. In order to correctly use the new technologies, a specific competency and skills should be developed and implemented: as it happens for the achievement of positive results in the ICU setting, the entire team (perfusionists, nurses, and doctors) has to be trained and should have specific knowledge of the new technologies. Moreover, in this time where the adequate allocation of resources appears to be very important, it is mandatory that the indications for the use of expensive and long-lasting techniques should be accurately weighed and shared among professionals.

The aim of this book is to provide readers with the theory and practical issues that experts in the field of extracorporeal circulatory and respiratory support believe could help in understanding and improving the practice of this medical device.

Milan, Italy

Roberto Fumagalli

Preface

Extracorporeal membrane oxygenation (ECMO) is not a new technique. It has been used in clinical practice for the last four decades, but the complexity of management and the relevant complications limited its diffusion to few specialized centers.

In recent years, the development of new materials and the simplification of the procedure led to a dramatic increase in the centers providing extracorporeal life support (ECLS) and in the number of ECMO runs, for both respiratory and circulatory indications.

A growing number of publications on all aspects pertaining to ECLS are populating the medical literature.

Despite this expansion in the use of ECLS and in ECLS-related research, the clinical management of ECMO remains mainly based on local protocols and procedures, and guidelines are lacking on many aspects of this practice. The ELSO (Extracorporeal Life Support Organization) registry and website, together with their so-called Red Book, represent the most authoritative resource, and many websites provide protocols and management guidelines from different ECMO centers. Still, such indications are mainly locally based or not regularly updated.

For this reason we tried to collate the most relevant aspects pertaining to ECLS, following two different approaches. Some chapters present an in-depth analysis of the current evidence and literature on the different indications, while other chapters face technical aspects with a more practical approach. These latter chapters are obviously influenced by the practice in the authors' centers, but we tried to integrate this with literature and different experiences whenever possible, particularly for the aspects where centers' attitudes diverge, such as left ventricle venting, cannulation techniques, and management of the lung during respiratory support, to name some.

ECLS remains a fast-evolving technique and some aspects still need research and optimization. Some of these are outlined in the conclusive chapter of the book, but more are still to be faced. Ample bibliographic references are provided at the end of every chapter for the interested reader to further explore specific aspects.

ECLS represents a relatively easy technique, but it is not simply a "procedure" to be learned and performed. ECMO is an excellent tool for organ support, but it requires sound physiologic and pathophysiologic knowledge and needs to be combined with top-level standard care.

We are aware that, as a first edition, the readers will find aspects of the book that might be improved, and we will welcome any suggestion in this regard. We still hope that the present work will be useful in disseminating ECLS knowledge and stimulate further study and research.

Fabio Sangalli, Nicolò Patroniti, Antonio Pesenti, Monza (MB), Italy

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Part I

History and Technical Aspects

History of Extracorporeal Life Support

1

Fabio Sangalli, Chiara Marzorati, and Nerlep K. Rana

ECMO (extracorporeal membrane oxygenation), also called ECLS (extracorporeal life support), in its actual application is an evolution of the heart–lung machines used in cardiac surgery. Depending on its configuration – venovenous or venoarterial – it is used to support respiratory function, circulation, or both. This treatment provides a bridge, either to healing of the natural organs or to long-term devices or transplantation. In fact, although ECMO has the capability to support cardiorespiratory function temporarily, it is not a cure for the underlying disease. As Warren Zapol, one of the fathers of respiratory ECMO, pinpointed in an editorial in the *New England Journal of Medicine* in 1972, the goal of ECLS is to “buy time” while sustaining an adequate tissue perfusion [1].

Despite the fact that the origins of ECLS stem from cardiac surgery and the heart–lung machine, its main applications – at least until recent years – and most of the related research were carried out in the setting of severe respiratory failure.

Artificial oxygenation is a theme that has always fascinated scientists since the beginning of modern medicine.

The first attempt to artificially oxygenate blood in an extracorporeal circulation was achieved in 1869 by Ludwig and Schmidt, by shaking together defibrinated blood with air in a balloon [2]. Next step was reached 10 years later, by artificially perfusing for the first time an isolated kidney using the first simple “bubble oxygenator.” In the same year, Frey and Gruber described the first “two-dimensional,”

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direct-contact extracorporeal oxygenator that exposed a thin film of blood to air in an inclined cylinder that was rotated at a frequency of 30/min by an electric motor [3–7].

Several bubble- and surface-type oxygenators were developed in the first two decades of the twentieth century. The main problems that hampered the development of the technique were thrombosis and hemolysis [8]. The turning point was the discovery of heparin by Jay Maclean, in 1916. This led to overcome most of the problems due to the contact of blood with air and the resulting prothrombotic activation [3, 4, 7].

The first whole-body extracorporeal perfusion was realized on a dog in 1929 by Brukhonenko and Tchetchuline in Russia [3, 7, 9–11].

Between 1930 and 1953 three important oxygenators were developed; they paved the way to apply the technique to men:

- The film oxygenator developed by Gibbon between 1937 and 1953 consisted of a stationary screen oxygenator [12–15] made up of a series of six to eight wire mesh screens arranged vertically and in parallel in a plastic container down which the blood flowed, forming a stable film that was exposed to a flow of oxygen [5, 11]. Kirklin et al. [16–19], at the Mayo Clinic in Rochester, Minnesota, further developed the Gibbon-type stationary screen oxygenator into the Mayo-Gibbon pump-oxygenator apparatus.
- The rotating disc oxygenator was described in 1948 by Bjork. It was further modified for clinical use by several scientists and improved with the development of materials.
- The bubble oxygenator was described in 1952 by Clarke, Gollan, and Gupta. They reported that although small bubbles with their large surface area to volume ratio favored oxygen uptake, they were less buoyant. This means that smaller bubbles are less likely to rise spontaneously to the surface and are more likely to remain in suspension – air embolism is therefore more likely. An optimum balance has therefore to be obtained. This optimum is believed to exist if the bubbles are between 2 mm and 7 mm in diameter. Alternatively, a mixture of small and big bubbles may be used. This oxygenator was subsequently modified and improved until the DeWall oxygenator, a “sequential bubble oxygenator,” i.e., its components (bubbler, defoamer, reservoir, and pump), are arranged linearly in series [7, 20].

The first successful extracorporeal cardiopulmonary bypass was performed in 1953, by the surgeon John Gibbon. In 1954, Gibbon described how the heart-lung machine could be used, in case of emergency, to support respiratory and circulatory activities. This theoretical intuition clashed with the practical impossibility of extending the duration of extracorporeal circulation over 6 h. This was mainly due to the cellular damage caused by the direct exposure of blood to gas. Interposing a gas exchange membrane between the blood and the gas flow solved most of this problem, and with this technological innovation the machine became more effective, allowing to perform ECMO for longer periods.

The first successful use of prolonged life support with a heart-lung machine was conducted by J. Donald Hill in 1971. The patient was 24 years old affected by post-traumatic ARDS, who was supported with ECMO during the acute phase of his



Fig. 1.1 The first successful ECMO patient

pathology, for 3 days. The patient was eventually weaned from ECLS and survived (Fig. 1.1) [21].

This success was of fundamental importance for the subsequent development and spread of ECMO. In the same period, ICUs were developing and hemodialysis was introduced for the treatment of acute renal failure. ARDS remained a fundamental issue for critically ill patients, and the ECMO success was a hope for a definitive solution to this problem: thanks to that treatment physicians could allow the functional recovery of the damaged lung. The interest linked to ECLS treatment was especially about its effectiveness as a respiratory support. This led to the creation of the name ECMO (extracorporeal membrane oxygenation), which emphasized the aspect of artificial oxygenation.

In 1975 Bartlett successfully treated with ECMO the first newborn, a baby called Esperanza. The success of this case led to a great enthusiasm, and in the following years a lot of other patients, both pediatric and adults, were effectively treated with ECMO [22]. In 1974 the Lung Division of the National Heart and Lung Institute started a large multicenter trial to test ECMO versus conventional therapies in acute respiratory failure. The results were disappointing, with just 10 % survival in both groups and no significant difference between ECMO and conventional therapy [23].

The results of the NIH trial led to a diminished attention to ECMO, but a few centers continued improving the technique (Fig. 1.2).

In 1978 Kolobow and Gattinoni introduced a modified extracorporeal gas exchange technique, called extracorporeal carbon dioxide removal (ECCO₂R). The

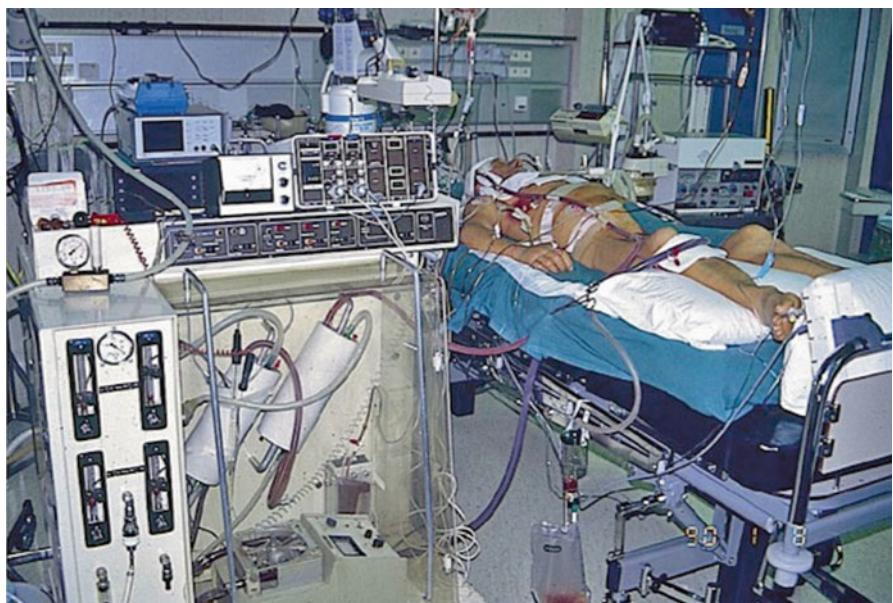


Fig. 1.2 VV ECMO in Monza, early 1990s

rationale of this technique was to reduce CO_2 to decrease ventilation to the minimum necessary to recruit alveoli. The new ECMO was performed at low extracorporeal blood flows (20–30 % of cardiac output), so that a venovenous bypass technique instead of a venoarterial one sufficed, which turned out to be less detrimental to blood cells, coagulation, and internal organs. Using LFPPV–ECCO₂–R, Gattinoni et al. reported survival rates of up to 49 %. In the following years several centers corroborated the promising survival rates of around 50 % and higher [14, 24–27].

The need for a coordination between ECMO centers led to the foundation in 1989 in New Orleans of ELSO (Extracorporeal Life Support Organization), a free community of clinicians and researchers, with the aim to collect data from the ECMO centers on a unique database and to standardize the procedures.

The evolution of venovenous and venoarterial ECMO diverged over time, with VV ECMO consolidating its primary role in respiratory support and VA ECMO assuming an increasing role in the advanced management of circulatory failure.

1.1 VV ECMO

After a period of “disgrace,” mainly due to the relevant complications and to the appearance on the scene of new promising and – apparently – less invasive strategies, namely, inhaled nitric oxide and prone positioning, VV ECMO was subject of

a renewed interest after the publication of CESAR Trial [15]. This is a multicenter study comparing conventional therapies to VV ECMO support in ARDS. Results showed a higher survival and less disability at 6 months in the ECMO group. Moreover, although not the primary outcome, an actual difference in survival of around 25 % was observed for patients considered for ECMO treatment at 28 days, the primary outcome of most ARDS literature.

Even if what this trial actually demonstrated was the importance of centralization of severe ARDS patients to a specialized center, this gave a great thrust to research, and in the following years the final explosion of the application of this extracorporeal support was due to the use of ECMO as a rescue therapy in Australia and New Zealand during the H1N1 influenza pandemic, proving its power in hypoxic emergencies [28]. The results obtained during this pandemic, more than any randomized trial, led to the worldwide acceptance of the use of membrane lungs.

This led to the creation of ARDS Network, a clinical network initiated by the National Heart, Lung, and Blood Institute, National Institutes of Health, developed in order to carry out multicenter trials of ARDS treatment.

Similar experiences, with excellent results both from a clinical and an organizational point of view, were realized in Italy [29] as well as in many other countries [30].

1.2 VA ECMO

Although VA ECMO was originally applied for respiratory support, its main application is nowadays as a circulatory support. In this setting, VA ECMO was employed almost exclusively as a support for postcardiotomic cardiogenic shock until recent years.

In the past few decades, VA ECMO gained a place out of the operating theater to become an advanced treatment for cardiogenic shock. As you will read in the following chapters, it is nowadays widely employed as a circulatory support for cardiogenic shock of any etiology. Its ease of application, which makes it possible to institute the extracorporeal support virtually anywhere, and the relatively low costs made it an appealing alternative to other mechanical circulatory support systems, especially in the emergency setting.

Another emergency application where ECMO gained a pivotal role as a unique option is that of refractory cardiac arrest. In selected populations, ECMO demonstrated an advantage in survival and neurological outcome in patients with an expected mortality approaching 100 % [18].

The development of miniaturized systems and more biocompatible circuits made it possible to bring ECMO everywhere in the hospital, to retrieve patients from hospitals without ECMO facilities (Fig. 1.3) or even out of the hospital [19, 31]. This was simply unimaginable just two decades ago, as Fig. 1.3 demonstrates clearly.



Fig. 1.3 Retrieval of an acute cardiogenic shock patient from a peripheral hospital

1.3 Conclusion

The technological evolution and new directions expand every day the potential of ECLS.

The relatively short history of ECMO is dotted with great discoveries and forward leaps and hampered with disillusionments, but – for sure – most of this story has yet to be written!

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Developing a New ECMO Program

2

Antonio F. Arcadipane and Giovanna Panarello

Since the first successful use of an artificial heart/lung apparatus by John Gibbon the extracorporeal circulation technique has been optimized, and its applicability expanded to multiple clinical settings, in recent decades, extracorporeal membrane oxygenation has become the first line of mechanical circulatory support for cases of severe cardiopulmonary failure not responsive to conventional therapy.

The diffusion of this complex technology in clinical practice and the good results in terms of morbidity and mortality explain the desire that many hospitals feel to exploit this treatment, though awareness of the technical skills and clinical competencies required for proper management of such an invasive and high-risk treatment has limited its application. Only highly specialized centers equipped with specific infrastructural characteristics, knowledge, experience, and organizational models are suited to make use of extracorporeal circulation.

Since the H1N1 pandemic influenza in 2009, and following the publication of the CESAR [1] trials results and the Anzic [2] study, the medical community has felt the need to increase the availability and the number of centers specialized in extracorporeal circulation.

This chapter is intended for health-care givers already expert in intensive care and willing to set up an ECMO program.

The Extracorporeal Life Support Organization (ELSO [3], an international organization founded in 1989) has published a list of recommendations and requirements that a center should satisfy in order to be recognized as suitable for managing extracorporeal support. These guidelines are reviewed and updated every 3 years to keep pace with the continuous improvement in technique and scientific understanding. All of the 240 international centers adhering to ELSO are required to meet the standards of ELSO's prerequisites.

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Though this treatment is burdened by intrinsic risks, the morbidity and mortality rates can be contained in centers with specific management protocols, careful selection of candidates for extracorporeal circulation support, and latest-generation technology. A learning curve is unavoidable, but certain technical, clinical, and scientific standards should be met before implementing an ECMO program.

The support of already experienced centers with recognized competence in the field is an essential aid, and their assistance during the learning phase, when sharing decision-making and programs may ensure better results, is crucial.

Specific steps can be identified in the set up of an ECLS program, and all the passages must be fully analyzed to obtain the best results before the program starts.

2.1 Organization

Ideally, an ECMO center should be located in a tertiary hospital where all ventilation modes and/or rescue therapies can be guaranteed. There should also be availability of rapid consultation by a wide range of specialists, which is often necessary for critical patients. According to the ELSO guidelines, the regionalization of a referring system, with predefined centers covering precise geographic areas, is advisable. Regionalization can have several advantages: from an organizational standpoint, it facilitates coordination of activity within a geographic area; from a clinical standpoint, it allows concentration of patient volume in specialized centers in order to guarantee at least six cases a year, the minimum recognized as sufficient for maintaining clinical expertise and better outcomes [4, 8, 9]. The relation among outcome, regionalization, and high-volume programs is even stronger for low-volume procedures performed in high-risk patients (such as ECMO candidates), and though the relation between outcome, ECMO, and population volume has never been formally addressed, we can deduce from studies done in highly specialized adult and pediatric ICU cases that centralization is an effective tool for optimizing results and costs.

2.2 Planning

Defining the scope of the program, and the role of the center, in the local health-care system is the first step in clarifying not only the duties but principally the limits of this highly complex clinical activity.

An exhaustive plan starts with an assessment of needs, which means verifying the requests from the medical community and defining which tools (human and instrumental) the new center should rely on to satisfy the request.

Assessment of needs consists of:

1. Identification of the manageable patient population
2. Identification of the personnel necessary to run the project
3. Evaluation of required equipment
4. Identification of financial support

2.3 Manageable Patient Population

The demand for the new center should be measured considering currently unmet needs and the potentially increasing request for treatment as soon as the project starts. A further consideration is proximity of potential referring hospitals. This is essential for better defining the volume of patients the referral center might be asked to respond to. Patients already managed by the referral center can also be the beneficiaries of the new program, though it is possible that an entirely new population of patients should be included.

At the outset of the program, a center may be not ready to manage all subtypes of extracorporeal support and all classes of patients. Age, disease requiring ECMO support, and already consolidated expertise should drive the starting choices. A lack of neonatal/pediatric expertise should not preclude the development of an adult ECMO service, and a cardiac surgery center, for example, could start by offering only cardiac ECMO support for respiratory cases. A wise starting point might be to begin with a select group of patients suffering from a specific disease with more predictable outcome, and only later expand the program to include patients affected with more complex clinical conditions, and with a higher risk of complications and less predictable outcomes [5, 6].

2.4 Identification of Personnel

In setting up a new ECMO program, a steering group must be identified. The components of the steering group are both medical and administrative personnel with responsibility of:

- Identifying the program's purpose
- Setting up the program
- Identifying achievable results and defining performance indicators, ideally compared with benchmarks of similar centers
- Implementing the program
- Defining a business plan for predicting expenses and potential revenues, not only monetary (QUALY adjusted) [11].

2.5 Staff

For an ECMO program to be developed, a dedicated team, led by a coordinator, must be available daily for 24-h coverage. Supportive personnel is important: consultants and rehabilitation specialists are of extreme value in meeting the needs of ECMO patients, both during and after the Extracorporeal circulatory support.

2.5.1 Coordinator

At least one ECMO coordinator (the ideal number of leaders will depend on the volume of ECMO service activity) should be designated. Part of this responsibility

is the identification of skilled personnel, the selection of equipment instrumentation, the organization of periodic and repeated in-services with technical and scientific updates, verification of expertise and competency, and organization of daily operational activity.

An additional duty of the coordinator is to oversee the drafting of protocols addressing the following topics:

- Indications and contraindications
- Clinical management of patients during ECMO, including weaning and decannulation
- Maintenance of equipment and updates in technologies
- Interruption of ECMO support
- Follow-up of patients after decannulation

2.5.2 Team

An ECMO team should be staffed by intensive care physicians and intensive care nurses with working knowledge of management of ECMO patients. Some centers will be able to include cardiothoracic surgeons and perfusionists in the ECMO team, though this is not mandatory.

The multidisciplinary composition of the team, with the constant presence of a cardiothoracic surgeon, is certainly an added value, though the absence of such a condition will not preclude development of an ECMO service if rapid consultation by a cardiovascular surgical service is ensured so that vascular-hemorrhagic complications can be immediately addressed. The final composition of the team must be based on the scope of the ECMO service. If the plan is to offer extracorporeal cardiopulmonary resuscitation (ECPR) and/or VAD support as a bridge to transplantation along with the ECMO support, cardiac surgery expertise must be included in the ECMO staff [7].

Experience in percutaneous, large-bore vascular access placement and extracorporeal circulation management is a required competency in the core group of an ECMO team. Similarly, technical skills in managing emergency troubleshooting (clinical and/or instrumental) are also requisites.

Physicians selected to be components of an ECMO team must have vast critical care experience and the working knowledge required for proper clinical management of patients suffering from end-stage organ disease. This means robust clinical and scientific training and knowledge of respiratory and cardiac failure in order to guarantee the most appropriate patient management, particularly in the period immediately preceding extracorporeal support placement, when candidates are more fragile and major disabilities and irreversible organ damage can occur. ELSO has not produced specific recommendations to define the expertise level required for ECMO specialists, thus leaving each center the autonomy to define competence. Each component of the team can have different roles and discrete autonomy in activity according to a recognized competency. An inclination for teamwork, a multidisciplinary approach, and, principally, the ability to transfer know-how are also essential.

The final composition of an ECMO team is not defined by any clear-cut indications, but is generally the result of organizational and financial consideration specific to each center. As already mentioned, a perfusionist may not always be involved. In Europe and Australia, critical care nurses with additional training in extracorporeal circulation play a central role. However, the ideal condition for rapid implementation of an ECMO service and optimal resource management may be found in post cardiac surgery intensive care, where medical and paramedical staff already possess the necessary knowledge to ensure a successful program of extracorporeal support.

Bedside care is not based on a fixed model and depends mainly on staff organization and the volume of patients, so that in some circumstances, it may become necessary to have a dual-provider model to ensure full-time exclusive supervision of both the patient and the ECMO circuits.

The staff selected for in-house management of patients on extracorporeal circulatory support may not always have the necessary technical skills and/or resources for interhospital transfer, so it may be necessary to rely on the collaboration of other centers.

2.5.3 Supportive Personnel

Consultants who are expert in a wide range of specialties outside the intensive care unit may become necessary while managing critical patients on extracorporeal circulatory support. Being located in a tertiary intensive care unit can facilitate the rapid assistance of necessary consultants and ensure the support of services essential not only during, but even after, an ECMO run.

According to the expectations of a tertiary level intensive care unit, daily around-the-clock availability of the following services must be guaranteed:

- Clinical laboratory
- Blood bank
- Radiology department ensuring necessary instrumentation for bedside radiologic and fluoroscopic exams
- Operating theater equipped for cardiothoracic surgery (indispensable for managing patients requiring cardiorespiratory support with VA ECMO)

Special consideration must be given to rehabilitation services: physical and respiratory therapies. In some lung transplant centers, the current tendency is to have ECMO-supported patients awake and extubated, making rehabilitative measures extremely important. Surviving patients could have clinically significant respiratory and musculoskeletal disabilities requiring long-term rehabilitation.

Finally, a nutrition support service needs to be involved because of the patient's decline in nutritional status, body composition changes, and sarcopenia, a relevant problem in critically ill patients, and even more significant in patients with respiratory failure [12].

2.6 Evaluation of Necessary Equipment

Because of rapid advances in ECMO technology, selection of equipment should be based not only on clinical considerations but also on the awareness that there may be investment in equipment that will soon be outdated. A criterion to be followed is the aim toward uniformity of materials, since this will facilitate staff training, enhance familiarity with equipment, and reduce the risk of error. Specialized technical support is often required for such sophisticated technology. A perfusion service and/or biomedical engineering department can be responsible for material revision and maintenance, but agreement with the seller company may be needed for maintenance and replacement of equipment.

The actual case load is the first criterion for determining the minimum necessary storage, though if a sudden rise in activity can be anticipated, additional supplies must be guaranteed.

Essential available endowment consists of backup components of the ECMO system and circuits and instrumentation (including a light source) to support bedside surgical procedures, such as surgical revision of cannulas or management of hemorrhagic complications. If a central ECMO has been placed, instrumentation for immediate surgical reopening of the chest must be ready and personnel trained in management of such complications available.

2.7 Identification of Financial Support and Cost-Benefit Ratio

ECLS requires highly sophisticated technology, is labor intensive and resource dependent, and requires highly specialized personnel, all of which determine the entity of financial support to be planned in the early phase of program development. A clear business plan should define the necessary starting budget, the magnitude of which is based on the anticipated costs of equipment, supplies, infrastructure, and personnel. Less manifest might be the expectation of income and benefits deriving from an ECMO program. Revenue from ECLS will depend on the regional/national health-care system of reimbursement. The cost-benefit ratio for such high technology applied to often fatal diseases can be calculated by weighing the treatment expense against the survival rate and the number of quality-of-life years (QALY) after the treatment. In the neonatal setting, positive survival outcomes for ECLS patients have been clearly verified [13, 14]. The CESAR trial had similarly positive results in adult patients, with a 20 % better survival when ECMO, in place of conventional therapy, was used for ARDS [15].

2.8 Training

Similarly to what is advisable for the implementation of any new project, medical, nursing, and paramedic personnel must be trained from both the theoretical and practical points of view, and the acquired skills must be tested and verified repeatedly while running the program.

ELSO has dedicated a significant part of its scientific activity to the publication of valuable recommendations for setting up a comprehensive educational plan. It has published *Guidelines for Training and Continuing Education of ECMO Specialists* [4], the *ELSO Red Book* [10], and the *ELSO ECMO Specialist Training Manual*. The result has been the drafting by ELSO of specific educational requirements expected from ECMO specialists, though some deviation from ELSO guidelines can be expected because of regional-institutional organization and regulations. Moreover, it is quite common for each center to adopt local training programs consisting of didactic courses and hands-on training. According to the ELSO guidelines, an ECMO training course should last at least 1 week and should include 24–36 h dedicated to didactics and 8–16 h to hands-on training in order to review ECLS equipment components and functional checks, basic and emergency procedures, and patient safety.

Didactic courses must cover the following topics:

- Indications, contraindications, and evaluation of the risk/benefit ratio
- Pathophysiology of diseases requiring ECMO support
- Selection of the most appropriate ECLS support (VA, VV, VA-V)
- Physiology of extracorporeal membrane function, pathophysiology of oxygen delivery and consumption, and physiology of venoarterial and venovenous ECMO
- Knowledge of ECMO equipment, cannulas, circuits, and materials necessary for extracorporeal support
- Daily management of patients and circuits
- Identification and management of clinical and mechanical emergencies
- Weaning from ECMO, decannulation
- Coagulation
- Post-ECMO complications and post-ECMO outcomes

Each ECMO specialist is expected to attend training courses, be updated periodically, and review protocols and results. The level and depth of an educational program will be determined by the existing competencies in each center. The ECMO coordinator is responsible for the training of the ECMO team, as well as for the verification of level of competency, and compliance with standards, international and/or internal.

Sharing results and experiences with other established ECMO centers is an essential component of the training/updating process and offers a wider and more critical review of each activity. This will help ensure rectification of management defects and optimization of treatment modalities.

2.9 Architectural and Infrastructural Features

Hospital infrastructures must be able to accommodate both the patient and the entire kit of devices required for clinical management over the ECMO run. The ideal available space for a single patient should be about 22–26 m² according to the structure of the intensive care unit, whether it be open space or single room. The number of sockets and sources of medical gas and air supply available in each patient location must be adequate to ensure proper functioning of all devices required to support vitals.

Intrahospital transport routes are further factors to be considered while assessing fitness of the ECMO center. Patients might need to be moved from one unit to another, and the access route should never be impeded by architectural barriers.

Adjunctive equipment might become necessary over the ECMO run and include those for renal replacement therapies, plasmapheresis, nitric oxide supply, and intra-aortic balloon pump counterpulsation. Space and infrastructure should never limit a proper clinical approach to the patient.

Space scheme and proximity must be considered. Rapid access to storage areas where equipment and devices can be placed is essential.

With the encouraging results obtained over the last 10 years, and the increasingly simplified use of latest-generation miniaturized devices, extracirculatory support is bound to become more widespread. In any event, it is essential that the human and material requirements reported in this brief chapter are met in order to help guarantee the success of a newly implemented ECMO program.

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Basic Aspects of Physiology During ECMO Support

3

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3.1 Introduction

Every life form, except for *Archaeabacteria* [1], relies on cellular respiration to create vital energy; hence, it consumes oxygen and produces carbon dioxide. Since gases move always downstream partial pressure gradient, life can only exist if oxygen diffusion is continuously guaranteed from the outer ambient to the mitochondria of each cell and the reverse for carbon dioxide [2]. This process is also called “the oxygen cascade.” In unicellular organisms, gas homeostasis is achieved by simple transmembrane gas diffusion. Contrarily, multicellular organisms had to develop complex cardiorespiratory systems to absorb, transport, deliver, and eliminate vital gases.

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The mainstay of modern intensive care medicine is to guarantee the function of the cardiorespiratory system. Extracorporeal membrane oxygenation (ECMO) represents nowadays the only therapy capable of completely replacing these vital functions.

ECMO consists of a life support technique based on the patient's venous blood diversion towards an artificial gas exchanger, which provides blood oxygenation and decarboxylation. Subsequently, arterialized blood is returned to the patient. Blood stream can be redirected to either the arterial or the venous circulation, through a central or peripheral vessel cannulation. In the venoarterial setting, the membrane lung (ML) is in parallel to the natural lung (NL) and the extracorporeal blood pump provides circulatory support. In the venovenous setting, ML is in series to the NL and the blood pump does not support systemic circulation.

Thus, a venoarterial ECMO (VA ECMO) replaces both heart and lung function and can be applied for cardiac and lung failure [3], while venovenous ECMO (VV ECMO) substitutes only native lung function and is used for respiratory failure [4].

Management of ECMO support is the last frontier of applied physiology. A solid knowledge of hemodynamic and respiratory physiology is mandatory to take care of patients undergoing ECMO. In this chapter, a review of physiology essentials during ECMO support will be presented. A particular interest will be directed on oxygenation, decarboxylation, and hemodynamics during ECMO support, with the necessary distinction between VA and VV ECMO.

3.2 The Artificial Lung

During ECMO support, oxygen delivery and carbon dioxide removal are determined by a close interaction between the artificial lung performances, the natural lung (NL) function, and the cardiac output (CO) of the patient. The gas transfer in the artificial lung is an essential step of this process.

A comprehensive description of mass gas transfer and membrane lung engineering goes beyond the scope of this chapter. We address the interested reader to other excellent publications on this specific topic [5]. We will introduce here the essentials for the management of patients undergoing ECMO.

Modern blood oxygenators are membrane gas exchangers and therefore are commonly called membrane lung (ML). They are comprised of microporous hollow fiber membranes, made of hydrophobic polymers (e.g. polymethylpentene). The sweep gas flows through the lumen of these fibers while blood flows on their outside. Differently from bubble oxygenators, membrane lungs avoid direct contact between blood and gases. Asymmetrical composite hollow fibers and heparin coated surfaces have been recently introduced to limit common problems encountered using first-generation membrane lungs, such as plasma leakage and coagulation activation; see Chap. 6 for more details.

Despite these technical progresses, developing a device capable of substituting the lung function is still a great technical challenge. This can be easily understood through a comparison between native and artificial lungs. In the native lungs, gases

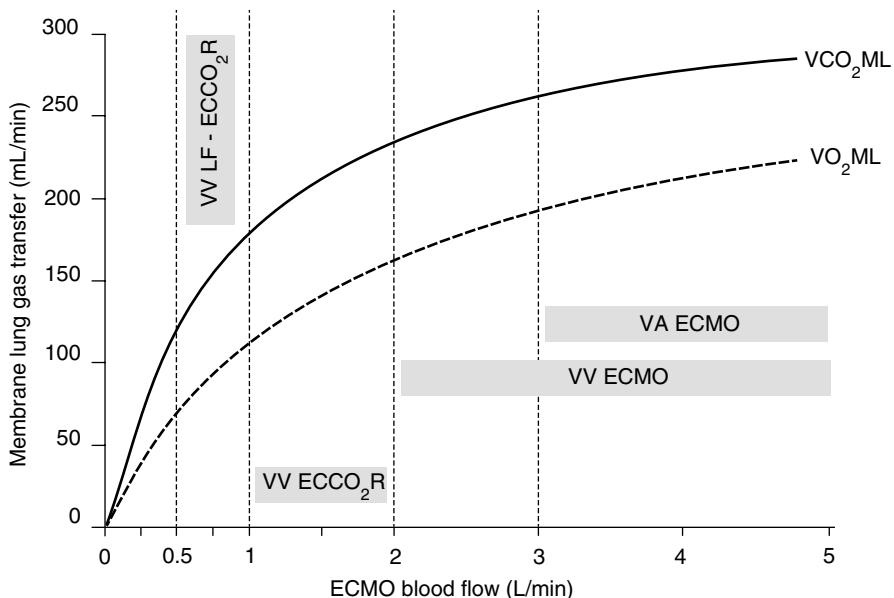


Fig. 3.1 Oxygen delivery (VO_2ML) and carbon dioxide removal (VCO_2ML) as a function of ECMO blood flow (BF). Operative range of BF of main CO_2 removal techniques is represented. $\text{VV-LF-ECCO}_2\text{R}$ venovenous low-flow extracorporeal CO_2 removal, $\text{VV-ECCO}_2\text{R}$ venovenous extracorporeal CO_2 removal, VV ECMO venovenous ECMO, VA ECMO venoarterial ECMO

move across the alveolar-capillary membrane, which is about 150 m^2 wide and $1\text{--}3 \mu\text{m}$ thick. This huge exchange area is compacted in a total volume of only 5 L, leading to a surface/blood volume ratio of about $300 \times \text{cm}^{-1}$. Under stress, human respiratory system is able to guarantee oxygen delivery (VO_2NL) and carbon dioxide removal (VCO_2NL) up to 3,000 mL/min [6].

In comparison, modern MLs are much less efficient. They have an exchange surface lower than 4 m^2 wide and a surface/blood volume ratio of $30 \times \text{cm}^{-1}$. In the artificial lungs, the interface between blood and gases is $10\text{--}30 \mu\text{m}$ thick. For these reasons, a ML provides a gas transfer just barely adequate for the metabolic requirements of a resting man. Indeed, even in the best conditions, oxygen delivery and carbon dioxide removal of 250–200 mL/min can be obtained through an artificial lung.

Gas transfer capabilities through ML are consequent to their intrinsic performances, which are directly proportional to the membrane surface area and dependent on hollow fiber characteristics, such as thickness and material. While these determinants cannot be altered at the bedside, the clinician can act on the blood flow (BF) and sweep gas flow (GF) to modify VO_2ML and VCO_2ML (Fig. 3.1).

Oxygen and carbon dioxide pressure gradients between the sweep gas flow and the blood are the fundamental determinants of the gas transfer. In turn, these pressure gradients are dependent on metabolism and blood transport of oxygen and carbon dioxide.

3.3 Oxygen

Normal oxygen consumption for a healthy adult at rest is about 250 mL/min (5–8 mL/kg/min). Oxygen consumption may significantly increase during exercise, shivering and fever, but also, less noticeably, with increased level of catecholamine (restlessness, pain, exogenous therapeutic administration), increased work of breathing and increased thyroid hormones. Conversely oxygen consumption is reduced by hypothermia, sedation, paralysis and hypothyroidism [7].

Oxygen is used in mitochondria for substrate oxidation, which leads to production of energy and carbon dioxide. Therefore, the oxidative metabolism generates the partial pressure gradient that drives the oxygen from the outer ambient to the cell mitochondria. Respiratory and cardiovascular systems are adaptive mechanisms developed by multicellular organisms to guarantee the oxygen supply to any single cell of the body.

We will follow the path of oxygen from the ambient air to mitochondria to elucidate the main physiologic aspects of oxygenation [8].

Partial pressure of oxygen of inspired gases ($pO_2\text{insp}$) is determined by the inspired oxygen concentration (FiO_2) and the barometric pressure (pB):

$$pO_2\text{insp} = \text{FiO}_2 \times pB$$

The alveolar partial pressure of oxygen ($pO_2\text{alv}$) is lower compared to $pO_2\text{insp}$ due to the added water vapor and the balance between oxygen removal by pulmonary capillary and oxygen replacement by alveolar ventilation.

Subsequently oxygen passes from the alveolar gas into the blood, mainly into the erythrocytes, by a passive diffusion process. In healthy lungs, diffusion is very efficient due to the extremely limited thickness of the alveolar-capillary barrier; therefore such equilibrium is easily reached.

The oxygen solubility in plasma is minimal (the coefficient of solubility is 0.003 mL/mmHg per 100 mL of blood); therefore with a normal arterial pO_2 of 100 mmHg, the oxygen dissolved in plasma is only 0.3 mL/dL, corresponding to an oxygen delivery of 15 mL/min, assuming a cardiac output of 5 L/min. Without hemoglobin, a cardiac output of 80 L/min would have been necessary to provide an oxygen delivery of 250 mL/min!

Fortunately, evolution has provided hemoglobin, which raises blood oxygen content exponentially, binding 1.39 mL of oxygen per gram if fully saturated (SatO_2).

Hence, total oxygen content can be calculated as

$$\text{O}_2\text{content} = (\text{Hb} \times \text{SatO}_2 \times 1.39) + (pO_2 \times 0.0031)$$

At a normal hemoglobin concentration, the arterial blood oxygen content is about 20 mL/dL.

Once the pulmonary capillary blood is loaded with oxygen, the cardiac output (CO) is regulated to maintain the systemic oxygen delivery (DO_2) at four to five times the consumption. Oxygen delivery is the arterial oxygen content times cardiac output, which is the oxygen delivered to the tissues each minute. DO_2 depends on cardiac output, hemoglobin concentration, hemoglobin saturation, and dissolved oxygen.

In the peripheral arterial capillary, hemoglobin releases oxygen. Following a pressure gradient, it diffuses through the endothelium, the intracellular space, and the cellular membrane, reaching its final destination, the mitochondria. In the mitochondria pO_2 ranges between 3.8 and 22.5 mmHg, but it varies between tissue, cells, and even regions of the same cell.

After transferring oxygen to the tissues, the capillary blood flows into the venous district where the oxygen content (CvO_2) may be computed as

$$CvO_2 = CaO_2 - \left(\frac{VO_2 \cdot NL}{CO} \right)$$

The right heart then drives the venous blood into the pulmonary circulation. There, venous blood is loaded of an amount of oxygen corresponding to that consumed by the tissues.

From the pathophysiologic point of view, the most important cause of acute hypoxic respiratory failure is maldistribution of ventilation (VA) and perfusion (Q). Following the three compartment lung model developed by Riley [9], the lung can be imagined as divided in three functional units characterized by different VA/Q ratios:

1. Ideal lung, without alteration of the natural coupling between ventilation and perfusion, having $VA/Q \sim 1$
2. Dead space, ventilated but not perfused alveoli, having $VA/Q = \infty$
3. Intrapulmonary shunt, perfused but not ventilated alveoli, having $VA/Q = 0$

In this model, gas exchange can happen only in the ideal alveoli. Dead space has important effects on carbon dioxide elimination (see later). Conversely, as an effect of shunt, the blood flowing through a pulmonary parenchyma with $VA/Q = 0$ does not participate in the gas exchanges and is not oxygenated. Hence, part of the venous blood mixes with arterial oxygen content and determines hypoxemia. The shunt is usually characterized as a ratio (Qs/Qt) between the shunted blood (Qs) and the total pulmonary perfusion (Qt).

When the Qs/Qt is higher than 0.4, even providing inspiratory fraction of oxygen up to 100 % is not sufficient to ensure an adequate oxygenation, and some degrees of hypoxia should be expected. If Qs/Qt is higher than 0.4, oxygenation provided by the native lung cannot sustain vital oxygen delivery. In these extreme clinical conditions, ECMO may prove to be the only clinical solution (Fig. 3.2).

3.3.1 Oxygenation During VV ECMO

When the natural lung is ineffective in oxygenating the blood, a VV ECMO support may be employed.

The global physiology of oxygenation during VV ECMO may be elucidated by following the changes in blood O_2 content along the circulatory system. Figure 3.3 is a schematic representation of a patient connected to a VV ECMO (panel a) and blood oxygen contents along the circulatory system (panel b).

Fig. 3.2 Partial pressure of oxygen in the arterial blood (PaO_2) as a function of pulmonary shunt (Q_s/Q_t), at various fractions of oxygen at the ventilator. If pulmonary shunt is higher than 0.4, vital arterial oxygenation may not be achieved even by 100 % oxygen supplementation at the ventilator

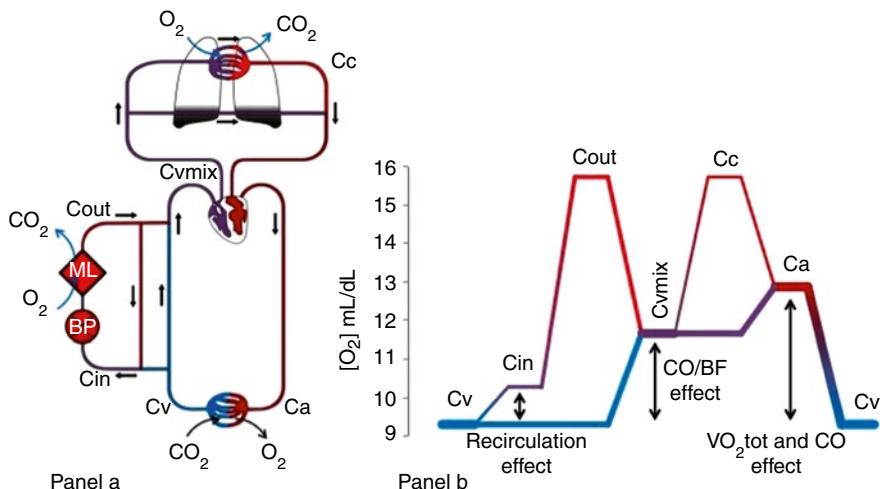
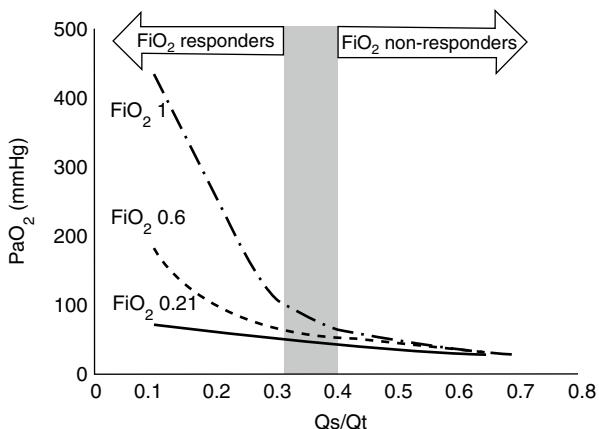
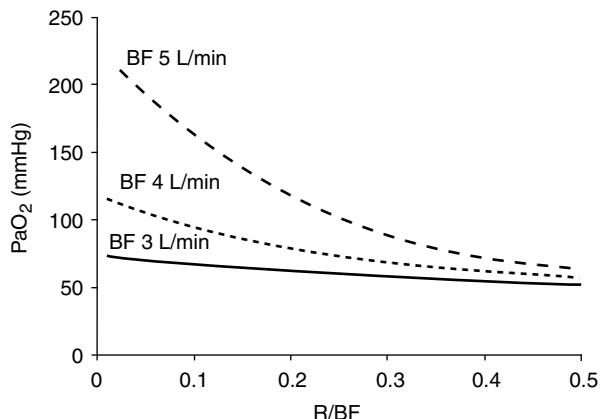


Fig. 3.3 Oxygen delivery and consumption during VV ECMO. Panel (a) The main determinants of blood oxygen content are represented. Oxygen content in the various blood compartments of the patient and ECMO circuit: Ca arterial, Cv venous, Cin circuit inlet, $Cout$ circuit outlet, $Cvmix$ mixed venous, Cc ideal unshunted pulmonary capillary. BP blood pump, ML membrane lung. Panel (b) Diagram representing the blood oxygen content of a patient (Hb 10 g/dL) connected to a VV ECMO support. The different sections of the venous, arterial, and extracorporeal circulation are distinguished by color and thickness. Blue lines represent deoxygenated blood, while red well-oxygenated blood. Thicker lines correspond to higher blood flows. Arrows represent the effects of recirculation ratio, cardiac output, and oxygen consumption on oxygen delivery during VV ECMO

Blood leaves the peripheral tissue with low oxygen content (CvO_2). The blood pump generates the extracorporeal blood flow (BF) diverging part of the venous return towards the ML. In this process, part of the already-bypassed flow is drained back to the extracorporeal circuit. This results in a recirculating blood flow (R),

Fig. 3.4 Partial pressure of oxygen in arterial blood (PaO_2) as a function of the fraction of the recirculating blood flow (R/BF) at different blood flows (BF). High recirculation fractions have extreme detrimental effects on the membrane lung oxygen delivery



which has detrimental effects on the oxygenation efficiency of VV ECMO (Fig. 3.4). Moreover, the R accounts for the difference in oxygen content between CvO_2 and the oxygen content of the blood entering the ML (CinO_2).

Then, the ML loads the extracorporeal BF with oxygen ($\text{VO}_{2\text{ML}}$) and raises the oxygen content in the outlet blood (CoutO_2), as follows:

$$\text{VO}_{2\text{ML}} = \text{BF} \times (\text{CoutO}_2 - \text{CinO}_2)$$

Subsequently, during VV ECMO, the blood returning to the right heart (the mixed venous blood, with oxygen content CvmixO_2) is an admixture of the deoxygenated venous return and the well-oxygenated extracorporeal blood. The important role of the interaction between CO, BF, and R in determining the respective influence of these two components will be described later.

The resulting effect of VV ECMO application is the increase of the oxygen content of the blood returning to the lung. Fundamentally, VV ECMO improves arterial oxygenation increasing oxygen content of mixed venous blood.

CvO_2 is eventually increased to CaO_2 by the residual oxygenating capacity of the NL. The oxygen added to the blood by the natural lungs ($\text{VO}_{2\text{NL}}$) is calculated as

$$\text{VO}_{2\text{NL}} = \text{CO} \times (\text{CaO}_2 - \text{CvmixO}_2)$$

The sum of $\text{VO}_{2\text{NL}}$ and $\text{VO}_{2\text{ML}}$ is equal to the total oxygen consumption of the patient:

$$\text{VO}_{2\text{Tot}} = \text{VO}_{2\text{ML}} + \text{VO}_{2\text{NL}}$$

Since most of the oxygen is transported bound to hemoglobin, the oxygen content of blood is highly dependent on the concentration and saturation of hemoglobin. An effective strategy in increasing DO_2 , after optimizing the ML and NL function, is increasing the hemoglobin concentration [10].

We will now address the roles of $\text{VO}_{2\text{ML}}$, CvmixO_2 , and $\text{VO}_{2\text{NL}}$ in determining arterial oxygenation during VV ECMO.

3.3.1.1 VO₂ML

The capacity of the ML of transferring oxygen is mainly determined by three factors:

1. The intrinsic properties of the ML affect the oxygen passive diffusion from the sweep gases into the blood.
2. The partial pressure gradient of oxygen between blood and sweep gases. The oxygen partial pressure in the sweep gases is determined by the FiO₂. The oxygen transfer through the ML is affected by the ventilation/perfusion matching, the hemoglobin concentration, and the transit time. When the oxygen partial pressure increases in the blood crossing the ML, hemoglobin becomes fully saturated, and little additional oxygen, physically dissolved, can be further loaded; therefore also an additional increase in GF will determine a minimal increase in the ML oxygen delivery. On the blood side, PinO₂ and the resulting SinO₂ highly affect the VO₂ML. Recirculation, increasing PinO₂, may vastly reduce VO₂ML (Fig. 3.4).
3. The extracorporeal blood flow is the major determinant of VCO₂ML. Indeed, increasing the extracorporeal BF determines linear augmentation of VO₂ML.

3.3.1.2 SvmixO₂

During VV ECMO, SvmixO₂ is mainly determined by the oxygen saturation of the blood leaving the tissues (SvO₂), the ratio between BF and CO, and the presence of recirculation (Fig. 3.5).

As previously said, an increase in BF at constant CO and R always determines an improvement in arterial oxygenation and tissue oxygen delivery.

More complicated are the effects of CO changes on oxygen delivery and arterial oxygenation. Assuming stable BF and R, patients with elevated CO necessitate higher BF to achieve normal arterial PaO₂ levels (Fig. 3.6, panel a). This does not necessarily mean that a lower cardiac output is desirable. Indeed, DO₂ depends on CaO₂ and tissue perfusion. During arterial hypoxemia, more than ever, an adequate

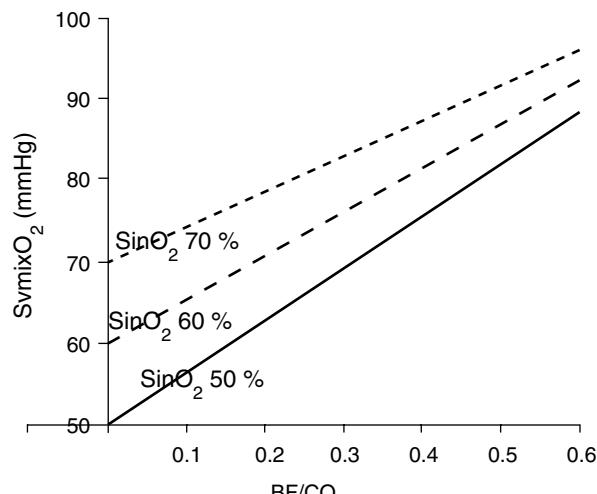


Fig. 3.5 Mixed venous oxygen saturation (SvmixO₂) as a function of blood flow/cardiac output ratio (BF/CO), at different oxygen saturation in the blood entering the ML (SinO₂)

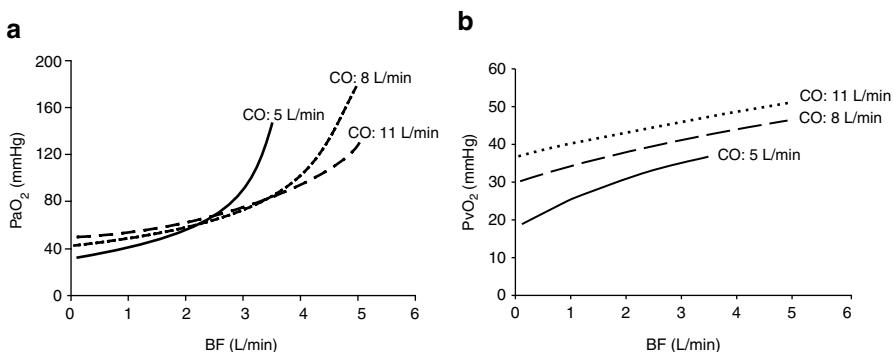


Fig. 3.6 The interaction between cardiac output (CO) and blood flow (BF). Panel (a) Partial pressure of oxygen in the arterial blood (PaO_2) as a function of blood flow (BF), at different cardiac output (CO). Panel (b) Partial pressure of oxygen in the venous blood (PvO_2) as a function of blood flow (BF), at different cardiac output (CO)

CO is essential to assure adequate oxygen delivery. Thus, increases in CO are usually associated with an increase oxygen delivery by the natural lung, assumed that the Q_s/Q_t is not changing. In this situation, a higher cardiac output provides higher- $\text{VO}_{2,\text{NL}}$, CvO_2 , and consequently PvO_2 (Fig. 3.6, panel b).

However, a rise in CO is usually a sign of augmented tissue oxygen requirements (e.g., fever, agitation, sepsis) and may change Q_s/Q_t and the R flow. During VV ECMO support, sudden changes of hemodynamic status are accompanied by complete alteration of the oxygenation steady state. Indeed, clinical experience teaches that in these scenarios CvmixO_2 and CaO_2 may unpredictably improve or worsen. Considering that many tissues have various oxygen requirements and vasculature, it is particularly difficult to predict the effect of a change in CO on oxygenation of different peripheral organs. Still, on this topic, scientific evidence is poor, and more research trials are needed [11] to better understand the complex pathophysiology of the effects of CO modulation on oxygen delivery.

3.3.1.3 $\text{VO}_{2,\text{NL}}$

The mixed venous blood is oxygenated according to gas exchange capability of the NL, which depends on the severity of the lung disease (mainly the intrapulmonary shunt fraction) (Fig. 3.7) and the ventilator setup (Fig. 3.8).

As clearly visible from Fig. 3.7, the worse the residual gas exchange capability of the NL, the higher BF and consequently cannula size are necessary. Indeed, if the intrapulmonary shunt is over 0.7, vital blood oxygenation can be obtained only by applying BF over 4 L/min. The use of adequately sized drainage cannulas is of paramount importance in this situation.

VV ECMO replaces, partially or completely, the function of the NL and allows reducing all the risk factors contributing to the onset of ventilator-induced lung injury: high ventilation volumes and pressures and high FiO_2 level. However, an extremely “protective” ventilator strategy, based on low levels of FiO_2 , PEEP and minute ventilation, may temporarily worsen the gas exchange function of the NL and therefore an increase in extracorporeal support is often required. The ventilatory strategy and the

Fig. 3.7 Partial pressure of oxygen in arterial blood (PaO_2) as a function of blood flow (BF), at different pulmonary shunts (Q_s/Q_t)

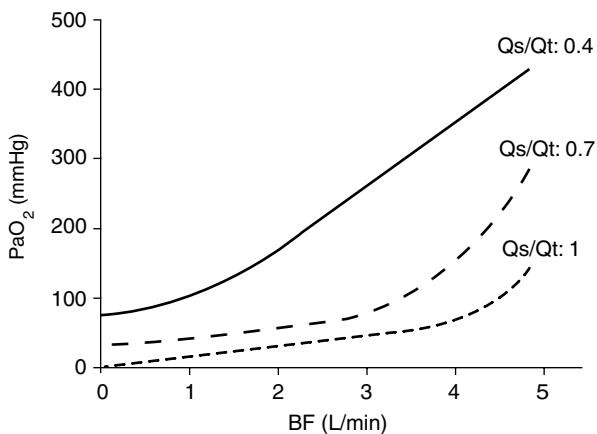
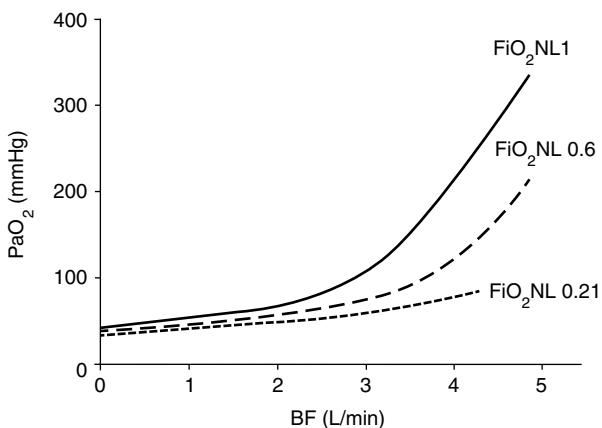


Fig. 3.8 Partial arterial pressure of oxygen (PaO_2) as a function of blood flow (BF), at various fractions of oxygen at the ventilator (FiO_2NL)



target oxygenation highly influence the required BF level and the choice of ECMO equipment and cannula sizes.

3.3.2 Oxygenation Support During VA ECMO

Particular attention has to be paid on oxygen delivery during VA ECMO support. No particular consideration is necessary until cardiac output is severely compromised, being all the oxygen delivery provided by the VA ECMO support. Complications may arise when lung function is impaired and a residual cardiac output is present, especially if a femoral arterial reinfusion cannula is used. Indeed, in this particular clinical condition, blood ejected from the left ventricle (not oxygenated by the compromised native lung) may perfuse the aortic arch and proximal aortic branches, determining coronary and cerebral hypoxia. Contrarily, the lower extremities will appear well perfused.

This “hypoxic Harlequin syndrome” [12] may be overlooked if the arterial blood sampling catheter is positioned in the femoral artery or in the left arm, while it is promptly recognized when the samples are collected from the right arm. It is hence important to position a right radial artery catheter to monitor heart and brain perfusion. If this is not feasible, at least an oximetry probe should be positioned on the upper right arm.

Potential solutions are increasing BF to limit LV ejection and conversion to a veno-venoarterial ECMO, by addition of an extra venous reinfusion cannula. The increase in BF may also paradoxically worsen lung function further, as discussed below. A low threshold for early direct LV venting should be maintained to protect not only the heart but also the lungs.

3.4 Carbon Dioxide

In resting condition, an adult healthy man produces approximately 250 mL/min of carbon dioxide value that is influenced by metabolic activity, core body temperature and caloric intake.

Carbon dioxide is the end product of aerobic metabolism. After being generated in mitochondria, following a series of partial pressure gradients, carbon dioxide passes through cytoplasm and extracellular fluid to the venous blood stream. Then, carbon dioxide is carried to the lung alveoli where it is released to the outer ambient.

The normal venous blood carries at least 55 mL of CO₂/100 mL, in three different forms: dissolved, as bicarbonate ions and in combination with proteins as carbamino compounds.

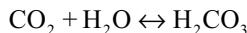
Dissolved CO₂ obeys Henry’s law, as follows:

$$\text{Dissolved CO}_2 \text{ content} = p\text{CO}_2 \times \alpha \text{ coeff}$$

where α coeff = solubility coefficient = 0.03 mmol/L × mmHg.

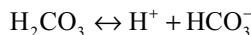
With a normal venous $p\text{CO}_2$ of 45 mmHg, at a temperature of 37 °C, dissolved CO₂ has a concentration of only 3 mL/100 mL of blood. Hence, dissolved CO₂ represents only 5 % of total CO₂ content.

Dissolved CO₂ reacts with water in blood to form carbonic acid, according to the following reaction:



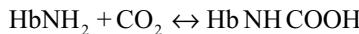
This reaction is extremely slow in the plasma (T½ ~ 1 min), while its speed is greatly increased in whole blood by carbonic anhydrase (also of 10,000 times), which is contained in red blood cells. Thanks to this enzyme, the conversion of CO₂ to H₂CO₃ requires less than 2 ms.

Subsequently, most of the carbonic acid formed in the red blood cells further dissociates into hydrogen and bicarbonate ions, according to the following non-enzymatic reaction:



About 70 % of CO₂ blood content is in bicarbonate ion form; indeed about 50 mL of CO₂ is carried in this form in 100 mL of blood.

Moreover, carbon dioxide also reacts with amino end groups of hemoglobin, forming carbaminic compounds as follows:



Carbon dioxide carried by carbamino compounds has a concentration of 3 mL/ dL in venous blood.

After being transported by venous blood to the pulmonary capillary, it readily diffuses to the alveolar space, passing through the alveolar-capillary membrane. Diffusion of carbon dioxide through this membrane is extremely efficient, and hypercapnia is indeed virtually never caused by altered diffusion capacity of the lungs. Consequently, alveolar partial pressure of carbon dioxide (alv pCO₂) can be considered usually equal to pulmonary end-capillary blood (ven pCO₂).

Hence, alv pCO₂ is the most important determinant of carbon dioxide removal from native lungs. Carbon dioxide is constantly added to alveolar gas by venous circulation and removed by alveolar ventilation, as follows:

$$\text{alv pCO}_2 = \frac{\text{VCO}_2 \text{ NL}}{\text{Alveolar ventilation}}$$

Alveolar ventilation is only the fraction of the inspired tidal volume that actually participates to the gas exchange, hence:

$$\text{Alveolar ventilation} = \text{Respiratory frequency} \times (\text{Tidal volume} - \text{Dead space})$$

Contrarily, the dead space is the component of the tidal volume not leading to effective gas exchange. Dead space may be further distinguished in apparatus, anatomical and alveolar dead space, which are respectively due to the presence of any external breathing machine, the patient airways and the unperfused alveoli. Alveolar dead space is defined as the part of the inspired volume that reaches the alveoli, but cannot take part to the gas exchange as consequence of altered ventilation/perfusion matching. Many clinical conditions are characterized by various levels of increased alveolar dead space, in particular pulmonary embolism, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). In these syndromes, the efficiency of carbon dioxide removal is altered. Consequently, the necessary CO₂ elimination is possible only at the cost of augmented alv pCO₂ or higher minute ventilation.

Both of these alternatives may not be desirable. Indeed, arterial pCO₂ is dependent on alv pCO₂, and an indiscriminate rise in pCO₂ has a strong impact on patient pH and may not be clinically sustainable. Moreover, augmenting minute ventilation is a well-known cause of ventilatory-induced lung injury (VILI).

3.4.1 Carbon Dioxide Removal During ECMO Support

All the clinical situations in which it is advisable to reduce alveolar ventilation or to avoid hypercapnia represent a potential indication for extracorporeal CO₂ removal. Hence, ECMO as a mean to remove carbon dioxide finds its clinical rationale to:

1. Reduce ventilatory needs and avoid VILI during ARDS [13]
2. Mitigate dynamic hyperinflation and hypercapnia during acute reacutezation of COPD [14] and status asthmaticus [15]
3. Bridge to lung transplant [16]

Removal of CO₂ during VV ECMO is much easier to achieve than oxygenation. With any type of ML, clearance of CO₂ is always more efficient than oxygen delivery (Fig. 3.2). As mentioned, most of the CO₂ content is transported in blood in the form of bicarbonate ion, with a total concentration of about 55 mL of CO₂ per 100 mL of blood. This means that 500 mL of venous blood contains an amount of CO₂ corresponding to the entire minute CO₂ production of an adult male (approximately 250 mL/min). Hence, during ECMO support, the entire patient CO₂ production may be removed with low BF. As an example, a conventional ML can readily remove 250 mL/min from an extracorporeal BF of only 1.5 L/min. This can happen only if high sweep gas flows (e.g. 8–15 L/min, according to the oxygenator characteristics) are used. Indeed, the gas flow is responsible for the removal of the carbon dioxide from the lumen of the hollow fibers of the membrane lung. Rising sweep gas flow of a membrane lung reduces partial pressure of CO₂ inside the hollow fibers, augments the partial pressure gradient in between blood and gas phase, and consequently augments CO₂ removal.

Hence, the amount of CO₂ transfer is relatively independent of blood flow while the sweep gas flow rate is its major determinant [17]. This strict relationship between carbon dioxide removal and GF dissociates membrane lung CO₂ removal from extracorporeal blood flow and has important clinical consequences.

First, during VV ECMO the clinician may selectively change carbon dioxide removal of the artificial lung by altering sweep gas flow, maintaining oxygen delivery unaltered. Through this intervention, ventilatory drive of the patient can be mastered and finely titrated to the desired level. As an example, in the most severe clinical conditions, extremely low tidal volume ventilation (and even apnea) can be achieved through elevated sweep gas flows [18]. Conversely, during weaning, a residual ventilatory drive can be maintained and spontaneous breathing guaranteed using a more moderate gas flow [19].

Second, several new devices have been recently implemented to perform low-flow extracorporeal CO₂ removal with less invasiveness and side effects compared to ECMO aimed at oxygenation support [20, 21]. These new technical approaches can be employed in all those clinical situations where controlling ventilation is necessary, while oxygenation is not an issue.

Third, new techniques aimed at augmenting ML CO₂ removal capabilities by extracorporeal loco-regional acidification are under evaluation [22, 23]. These may permit to reduce required blood flows, minimize associated complications and permit a safer and broader use of extracorporeal CO₂ removal.

3.4.2 Carbon Dioxide Removal During VA ECMO

Particular considerations are necessary for the management of carbon dioxide removal and ventilation during VA ECMO. Currently VA ECMO is mainly used to sustain circulation during cardiac failure. Namely, VA ECMO is applied in patients whose cardiac output is severely impaired and consequently have very limited lung perfusion, if any, from the pulmonary artery. In this condition, to conventionally ventilate the lungs has hence no physiologic rationale, since during VA ECMO the whole lung parenchyma is an alveolar dead space. Moreover, various studies suggest potential detrimental consequences of ventilation of unperfused lungs [24]. Contrarily, during VA ECMO, application of an adequate PEEP level and cyclically recruitment are generally suggested to avoid lung atelectasis. Continuous end tidal CO₂ monitoring is warranted to ensure adequate ventilation when a certain degree of venous return and right ventricular ejection is present.

3.5 Hemodynamics

The impact of ECMO on cardiovascular function depends mainly on two factors:

- Type of support (venovenous versus venoarterial)
- Site of vascular access (peripheral versus central, femoral artery versus axillary artery)

The main difference lies in the type of support, with a much less hemodynamic impact in VV as compared to VA ECMO. In VV ECMO the extracorporeal pump is functionally in series with the patient's heart, whereas in VA ECMO it is in parallel (Fig. 3.9).

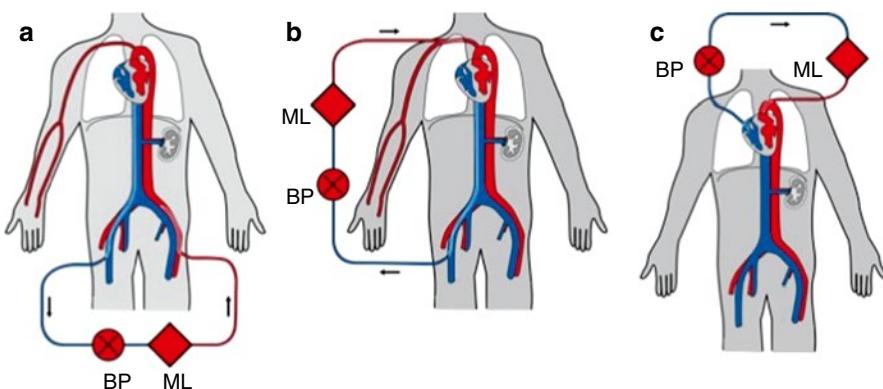


Fig. 3.9 Schematics of possible venoarterial ECMO circuits. (a) Peripheral, femorofemoral cannulation. (b) Peripheral, femoro-axillary cannulation. (c) Central cannulation. *BP* blood pump, *ML* membrane lung

3.5.1 Hemodynamics During VV ECMO

Irrespective of the site of cannulation, which can make a difference on blood gas dynamics, blood is drained from and returned into the venous system. This makes VV ECMO an in-series system with the natural circulation. No acute volemic changes happen, since the same amount of blood is continuously drawn and replaced.

The preload remains unchanged, as does the afterload of the left ventricle (LV). The energy balance of the myocardium is hence unaffected by the extracorporeal support. Even better, blood reaches the left heart much more oxygenated than normally, with a further possible advantage on myocardial perfusion. This venous “hyperoxia” may also help in reducing pulmonary vascular resistance (and hence pulmonary arterial pressure) by partially relieving hypoxic vasoconstriction. Hypoxia is a known risk factor for myocardial injury [25], and ECMO could act as a protective measure to prevent such injury. Despite this, sudden hyperoxia after hypoxia was associated with myocardial reperfusion damage in experimental models [26].

All these previous considerations stand for the conclusion that VV ECMO is a “hemodynamically neutral” support. This is largely true, but it is two faceted as every coin. VV ECMO is generally applied to very hypoxic patients, usually with elevated pulmonary vascular resistances and often with high cardiac output due to infection/sepsis. It is hence essential that the patient has a competent cardiovascular function, since the extracorporeal support does not provide any circulatory assistance. This must be assessed at the time of initiation and regularly assessed throughout the course of ECLS, to detect any worsening – due to sepsis or to any other cause – that may require conversion to a circulatory support.

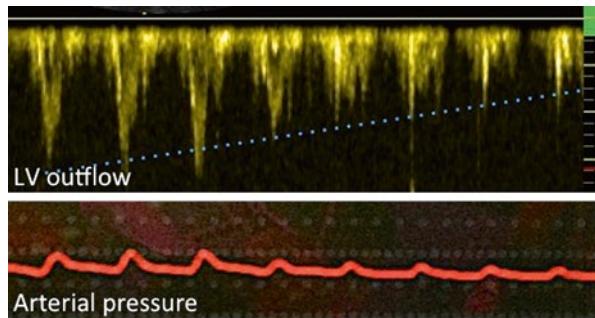
3.5.2 Hemodynamics During VA ECMO

Things become more challenging from a hemodynamic point of view when it comes to VA ECMO. Here the extracorporeal pump works in parallel with the patient’s heart. Systemic flow, therefore, is a combination of that established by the extracorporeal circuit plus the amount of blood passing through the native heart and lungs. This leads to a number of hemodynamic changes. Most of those occur irrespective of the cannulation site, while different arterial cannulation sites carry some peculiar advantages or disadvantages.

3.5.2.1 General Hemodynamic Changes

Loss of arterial flow pulsatility. Centrifugal pumps used for ECMO provide continuous flow. When the patient’s circulation is fully supported, natural ejection is almost abolished and the arterial pressure line becomes flattened as more blood is routed through the extracorporeal circuit (Fig. 3.10). The effect of continuous versus pulsatile flow on organ perfusion has been extensively investigated, and no definitive conclusion has been drawn to date on its potential negative effects. Both clinical and laboratory parameters have shown a possible advantage of pulsatile

Fig. 3.10 Reduction in LV ejection and loss of arterial pressure pulsatility at the increase of ECMO blood flow



compared to non-pulsatile perfusion on cardiac, renal, and pulmonary function [27]. However, no clear advantage has been demonstrated to date on mortality [28]. A certain degree of pulsatility – index of LV ejection – should however always be promoted and maintained to prevent stagnation of blood in the left chambers and the formation of intracardiac clots and the ensuing embolic risk. When this is not accomplished with low-dose inotropes or with a slight reduction in pump flow, venting is required. These aspects are widely discussed in the relevant chapters. A potential benefit in this regard has been postulated for the concomitant use of IABP [29, 30]. Together with reduced LV afterload and increased coronary perfusion [31], the preservation of a pulsatile flow waveform represents the rationale for aortic counterpulsation during VA ECMO. Despite potential relevant benefits, the evidence for the use of IABP in this setting is still weak, and at the moment potential disadvantages limit its widespread use.

Reduction of preload. VA ECMO diverts most of the venous return to the right heart into the extracorporeal circuit. This effect is beneficial for resting the right ventricle. The drawback of this reduction in pulmonary blood flow is that the coronary arteries are perfused mostly with desaturated blood coming from the bronchial circulation, leading to potential myocardial ischemia.

Increase in LV afterload. The reintroduction of blood into the arterial system leads to an increase in LV afterload that is directly related to the EC blood flow and only marginally influenced by the cannulation site. This may lead to inadequate drainage of the LV that may become distended. This in turn increases myocardial energy demands and may worsen ischemia and increase pulmonary congestion with deleterious effect on the lung. In an attempt to reduce such distention, pump flow is frequently increased to optimize venous drainage. This might paradoxically worsen LV distention due to a further increase in afterload. Strategies to reduce LV afterload and distention are discussed elsewhere in the book and aim at increasing natural ejection with inotropes and counterpulsation or – when this is unfeasible – to directly unload the LV via either a percutaneous or surgical approach.

3.5.2.2 Peculiar Hemodynamic Changes Depending on the Cannulation Site

Peripheral ECMO represents by far the most common configuration, and the femoral artery is the preferred cannulation site in adults. Nevertheless, other possibilities exist. Namely, central cannulation may be needed, with the arterial cannula placed

in the ascending aorta. In peripheral ECMO, the axillary artery might also be cannulated, while the carotid artery is not used in adults.

With respect to hemodynamic perturbations, the only difference from femoral access is that both aortic and axillary cannulations provide antegrade flow and that the coronary arteries are perfused by well-oxygenated blood coming from the extracorporeal circuit, so avoiding the risk for myocardial ischemia. This may also constitute a theoretical advantage over femoral cannulation when IABP is used during ECMO, but this is still uncertain.

Specific advantages and disadvantages of the different cannulation sites not pertaining to hemodynamics are discussed in the relevant chapters.

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Percutaneous Cannulation: Indication, Technique, and Complications

4

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and Michela Bombino

4.1 Introduction

Achieving proper vascular access is a fundamental step in implementing extracorporeal support, both for cardiac (venoarterial, VA ECMO) and respiratory (veno-venous, VV ECMO) assistance. Vessel choices, ECMO cannula types and sizes, and cannulation techniques are mainly dictated by the anatomical features of the vascular tree and the skills of the implanting personnel. In the early 90s, with the availability of thin-walled cannulas, cannulation techniques moved from surgical to percutaneous in almost all the cases. A historical perspective outlining the steps of this move will be given.

The percutaneous cannulation technique for venous and arterial ECMO accesses and its indications and complications will be outlined in this chapter, while the surgical cannulation technique will be discussed in Chap. 5.

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4.2 History of ECMO Cannulation Techniques

Prolonged ECMO support had its move from the cardiothoracic scenario; therefore surgical cannulation with VA configuration was implemented in the early years also in patients with pure respiratory failure [1, 2]. Thereafter, the VV configuration was preferred in the extracorporeal support of patients with acute respiratory failure. The technique described by Gattinoni et al. in 1979 [3] involved a femoro-jugular approach: the common femoral and internal jugular veins were surgically cannulated both centrally and distally; the blood was drained from the two catheters in the common femoral vein and from the distal catheter in the jugular vein and returned in the central internal jugular vein catheter. Continuous oozing of blood from the surgical wound was the rule, and daily revision of vascular sites accesses was required. Patient care and motility were difficult due to the multiple catheters and tubing at play [4]. Advances in the surgical technique were the development of a single-vein cannulation of the femoral vein through a double-lumen catheter [5] and the institution of sapheno-saphenous bypass [6]. The double-lumen coaxial catheter (Fig. 4.1) allowed the institution of an inferior vena cava-inferior vena cava bypass through a single surgical cutdown: the blood was drained from the external lumen of the double catheter and from the distal drainage from the leg and returned to the patients through the inner lumen. In the sapheno-saphenous bypass, the surgical plans involved were more superficial, and the distal venous drainage from the legs was maintained eliminating the need of distal cannulation; at ECMO termination the cannulas were removed with the ligation of the two saphena magna veins; no reconstructive surgery of the veins was needed.

In the 90s, with the advent of thin-walled spring-wire-reinforced catheters on the market, the first reports on percutaneous cannulation for cardiac and respiratory ECMO support were published [7, 8]. Since then, the percutaneous cannulation technique became the first choice in establishing vascular access for ECMO. The benefits reported were a shorter procedure time, almost null bleeding at insertion site if a coagulopathy was not present, a reduced risk of cannula-site infection, and a very simple decannulation [9].



Fig. 4.1 Historical picture of a handmade double-lumen coaxial catheter for institution of an inferior vena cava-inferior vena cava bypass through a single surgical cutdown

4.3 General Considerations for the Percutaneous Placement of ECMO Cannulas

The establishment and maintenance of adequate vascular access is essential for any type of ECMO support and can be achieved by percutaneous approach outside the operating room by trained personnel (intensivists, emergency department physicians, cath-lab cardiologists). Since a failure in cannulation would be critical for ECMO institution, a cardiothoracic surgeon or a vascular surgeon must be available on site to perform a surgical approach via a semi-Seldinger or a cutdown technique if difficulties in cannulation would arise. These problems are mainly related in the literature to the placement of the arterial cannula in VA ECMO for cardiac assist.

Patient size and ECMO configuration mainly dictate the choice of the ECMO cannulas. Different cannulas are available on the market for ECMO cannulation purpose. Recently a comprehensive review on this argument was published [10], and we will only summarize some cannula features that are important to know when choosing a cannulation site.

The manufacturer provide the specifications about the pressure drops generated at different flows to help choosing the right cannula for the specific clinical need [11]. For an adult patient of >70 kg weight in a VV configuration, venous drainage cannula ranges from 23 to 25 F, while reimmersion cannula from 19 to 21 F.

Vascular access for VV ECMO can be challenging in patients with a high BMI; in most of these patients, the femoro-jugular approach must be considered as the first choice. The same would apply to pregnant woman: in late pregnancy a 15–30° left lateral tilt position has been proposed to facilitate the insertion of the femoral cannula [12].

Vascular ultrasound has become invaluable for the localization of the vessels and measurements of their diameters [13, 14]. As a generic rule the size of the cannula must be no more than two-thirds of the vessel diameter, so that blood coming from the leg can flow freely around the cannula and venous drainage from the limb is not impaired. This is of greater importance when cannulation of the femoral artery is needed.

Some recent papers [15–19] describe the decision process in choosing a peripheral percutaneous approach, the cannulation techniques available, the equipment needed, and the procedure itself.

Choosing the vessels for access in VV ECMO must take into account:

- The maximum ECMO flow needed for the support of the patient
- The maximum recirculation tolerable
- The patient's comfort
- The anatomical difficulties or the presence of some obstructed vein

The size of the drainage cannula is the main determinant of ECMO blood flow, being flow directly related to the fourth power of cannula radius; the best position would be in the intrahepatic portion of the inferior vena cava or in the right atrium. Multiple holes are distributed along the cannulas to enhance blood drainage (multiple-stage drainage cannulas). The reimmersion cannulas normally have holes only in a short portion near to their extremity. There is no problem in choosing multistage

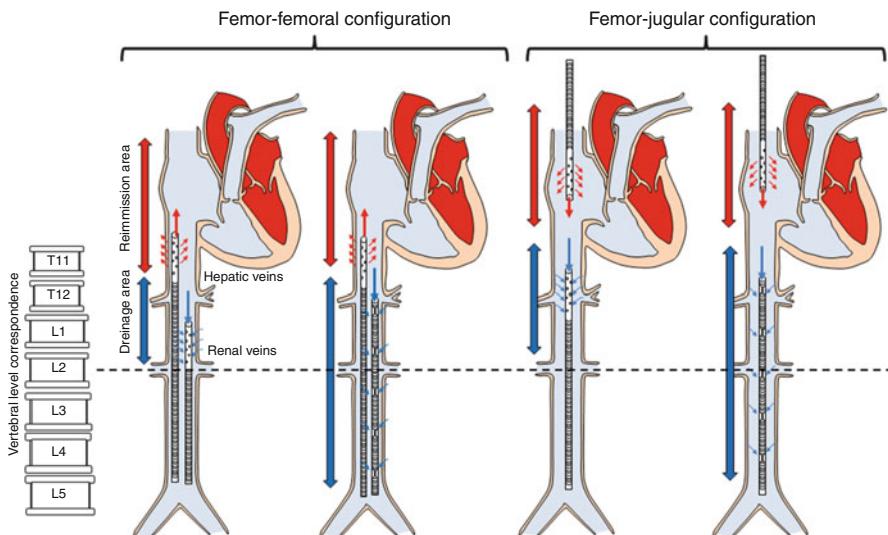


Fig. 4.2 Possible VV cannula configuration according to the type of drainage cannula (multistage side holes or cannula with side holes close to the tip) and to VV configuration (femoro-femoral or femoro-jugular). Correspondence between inferior vena cava main branches (hepatic and renal veins) and vertebral bodies is drawn. Independently from the reimmission cannula, tip of the drainage cannula should be positioned above renal veins, possibly in the intrahepatic portion of inferior vena cava. Multistage cannula should be used for drainage only especially in the femoro-femoral approach to minimize blood flow recirculation

cannulas both for drainage and reinfusion if a femoro-jugular approach is applied (Fig. 4.2), but if a femoro-femoral approach is chosen, a different kind of venous cannula must be used, because the side holes will generate a very high recirculation of oxygenated blood from the reimmission cannula to the drainage one (Fig. 4.2).

The configuration with the minimal recirculation is the femoro-jugular one [20]. Recirculation in the femoro-femoral approach can be minimized maintaining the drainage cannula below the diaphragm, above the renal veins, and the return cannula in the atrium or just below it (Fig. 4.2).

4.4 Preparation of the Patient for Percutaneous Cannulation

Before starting the ECMO cannulation procedure, in a nonemergent situation, an arterial cannula (a right radial arterial catheter if a peripheral VA femoro-femoral ECMO must be instituted) and a central venous catheter must be inserted for monitoring. Blood specimens are drawn to assess complete blood cells count, basal coagulation profile (PT, aPTT, fibrinogen, d-dimers, and ATIII if available), blood chemistry, and blood gases. According to the results, a request for packed red blood cells, platelets, or plasma can be forwarded to the transfusion service.

The nurse in charge for the patient prepares the chosen vascular sites according to the procedure normally used for other central accesses; hair removal is performed if necessary with a hair clipper maintaining the integrity of the skin.

The cannulation procedure must be accomplished with complete aseptic technique; thus at least two operators will perform surgical hand washing and will be dressed with maximal sterile barrier precautions, cap, mask, sterile gown, and sterile gloves. The skin at insertion sites will be prepared with chlorhexidine 2 % and the surgical field prepared with large drapes covering the entire bed allowing space for cannulas and tubing during the procedures [21]. At this time a shot of antibiotic (first- or second-generation cephalosporin) is advisable as prophylaxis during the procedure [22].

The material for cannulation is prepared on a serving trolley and comprises:

- A needle for venipuncture
- A J-tipped guidewire
- Dilatators (multiple or tapered)
- Surgical tools
- Sutures

4.5 VV ECMO Percutaneous Cannulation

Since the end of the 1980s, the percutaneous approach was introduced and can now be considered the first-choice technique [8, 15–19, 23, 24] for VV bypass. The surgical procedure has been almost completely abandoned, since this technique is more time-consuming and burdened with complications, uncontrollable bleeding representing the main one. The main advantage of percutaneous cannulation is a reduced risk of bleeding, but this technique also allows shorter operative time and a much easier mobilization and nursing of the patient.

Percutaneous cannulation of the femoral, jugular, and rarely subclavian vein is described in the literature. Axillary vein cannulation requires always a surgical technique.

The technique used for percutaneous cannulation is similar to the one introduced by Seldinger almost 60 years ago; for a detailed description, refer to the Lancet review published in 2005 [25].

4.5.1 Femoro-Femoral Approach

The two operators will localize the femoral veins below the inguinal ligament, and the procedure starts with the puncture of the vessels with an 18 G needle under ultrasound vision. We are used to introduce first an 8 French catheter sheath introducer into the femoral veins using the Seldinger technique and prepare a concentric purse-string suture around the insertion point in order to limit blood loss during the multiple dilatations of the vessels. A stainless-steel J-shaped guidewire (0.038 in. × 150–180 cm) is passed through the 8 Fr introducer; the guidewire must

be long enough to reach the inferior vena cava. After wire placement, a 2,500–5,000 unit heparin bolus is administered to prevent thrombosis in the cannulas. At this point vessel dilators of increasing caliber are passed subsequently over the guidewire in order to obtain the right dilatation for the chosen cannula. To avoid kinking of the guidewire, it is important that the wire moves freely within the dilator, one operator will maneuver the dilators while the other will maintain the guidewire aligned with the dilator and with a slight tension. To facilitate the dilatation of the vessel and minimize the risks of guidewire kinking, our group introduced some years ago a modified technique in which three guidewires were inserted in the same vessel [26]; a dilator was passed over each wire to obtain proper dilatation for the chosen cannula (e.g., if a 24 Fr cannula has to be inserted, an 8 Fr dilator was passed over each guidewire). The development of a single progressive tapered dilator (Dilator Coons Taper 4–22 Fr, Cook Medical, Bloomington, USA) allows now to reduce the dilatation step to the passage of a single dilator if a cannula up to 21 Fr must be inserted or a two-step dilatation if a larger cannula is needed. The quality of the guidewire is also crucial for the success of the maneuver; if the guidewire is too soft, the risk of kinking while passing the dilators is very high; we have good results with the use of the Amplatz Super Stiff™ Boston Scientific Guidewire.

After the proper dilatation is achieved, the cannula is inserted over its introducer; when the right position is achieved, the introducer and the guidewire are removed and a controlled filling of the cannula with blood is allowed by maintaining the extremity of the cannula slightly above the bed plane. The drainage cannula is inserted first and flushed with saline. Then the two operators move to the contralateral site, and the reimmersion catheter is inserted with the same technique. Both cannulas are then secured to the skin at least in two points.

The VV femoro-femoral approach carries a higher risk of *blood recirculation* compared to the femoro-jugular access; for this reason it is important to put the tip of the drainage cannula at the level of L1–L2, in order to receive the blood contribution of the renal veins, while the tip of the reimmersion cannula should be placed close to the junction between the inferior vena cava and the right atrium (e.g., at the level of T10–T11). In this way blood recirculation should be acceptably low, just around 10–15 % (Fig. 4.2).

A bedside imaging technique is therefore advisable to control the guidewire position and its shape during dilatations of the vessel and to guide the correct cannula position. Chest and abdominal x-rays are static and don't allow the rapid correction of cannula position during the procedure [27]. Ultrasound and fluoroscopy can be used during cannulation to optimize catheter placement. Ultrasounds are easily accessible at the bedside; patient's characteristics and expertise of the operator are the main determinants of adequate imaging [28]. Fluoroscopy would be the best imaging technique to visualize guidewire misplacements during cannulation [29] and therefore avoid ECMO cannula malposition, but is rarely available at the bedside and carries the risk of x-ray exposure, and with the new technological ICU beds, fluoroscopic vision of the entire procedure is sometimes very difficult.

4.5.2 Femoro-Jugular Approach

Another option to perform VV bypass is represented by the femoral-jugular approach. In this case one operator proceeds with the cannulation of the femoral vein as described above, and the other acts on the internal jugular vein. It's advisable to drain blood from the femoral cannula positioned in the inferior vena cava in order to minimize recirculation. The return cannula is positioned through the internal jugular vein proximal to the right atrium. Cannulation of the jugular vein carries the risk of pneumothorax, and this must be taken into account in choosing this site. A shorter cannula, if available, must be chosen to allow better fixation. The increasing implementation of VV ECMO in awake spontaneously breathing patients arises the warning about the risk of air embolism during jugular vein cannulation. Therefore some groups advocate elective intubation before the procedure and extubation thereafter [30].

4.5.3 Double-Lumen (Avalon) Cannula

The “two vessel approaches,” femoro-femoral and femoro-jugular, are not comfortable for the patients. Movements are limited, and an increased need of sedatives is reported.

A single-vessel approach has been recently applied also in the adult population through a double-lumen cannula available in different sizes ranging from 13 to 31 Fr [31–34]. This type of cannula allows both drainage and reinfusion. The cannula has to be introduced through the internal jugular vein, and the placement should be guided using fluoroscopy and ultrasounds [35–37]. The position is crucial; the cannula must cross the right atrium with the tip in the inferior vena cava. Blood is drained from both the superior and inferior vena cava while the reinfusion occurs through a separate lumen into the right atrium just facing the tricuspid valve. This cannulation seems to have good results [33, 34] and allows physiotherapy with a walking patient [38].

4.6 VA ECMO Percutaneous Cannulation

Percutaneous femoral cannulation for *venoarterial* VA ECMO is mainly an emergent procedure and can be performed everywhere in the hospital [39] and was recently performed also outside the hospital [40, 41]. While VV cannulation for respiratory assistance generally allows time for a safe procedure, VA cannulation for cardiac rescue requires to be accomplished in the shortest possible time, exposing to potentially fatal difficulties and complications. Nevertheless, the percentage of successful cannulation is very high, hovering in many studies over 90 % [42, 43]. We already stated above that the presence of a cardiothoracic or vascular surgeon is advisable on site during the procedure; after one or two unsuccessful attempts to locate and puncture percutaneously the vessels, a switch to an open technique is mandatory.

4.6.1 Implantation Technique

The preliminary identification of the femoral vessels using ultrasound can facilitate the task and allows a more careful selection of the cannula diameter according to the size of the vessel. The procedure is best performed with two operators, to control the cannulas and wires. The placement of femoral catheters is performed under aseptic technique and begins with percutaneous puncture of the femoral vessels. If the puncture is performed during CPR, both players may act simultaneously, trying to locate the femoral artery and vein. It is preferable to use both sides for cannulation whenever possible to minimize the chance of impaired limb perfusion. If time allows it is preferable to perform an ultrasound-guided procedure. Following the Seldinger technique, a flexible J-tip guidewire (0.038 in. × 150–180 cm) is advanced from the femoral vein into the inferior vena cava (IVC) directed toward the right atrium, and an Amplatz ultra-stiff J-tip guidewire (0.038 in. × 180 cm) is advanced from the femoral artery toward the aortic valve. After wire placement, a 2,500–5,000 unit heparin bolus is administered to prevent thrombosis in the cannulas. Using a single progressive dilator (Coons Taper 4–22 F, Cook Medical, Bloomington, USA), the venous and arterial accesses are progressively dilated and cannulas are subsequently introduced over the wire. The venous cannula is advanced till the cannula tip is in the mid-right atrium. The arterial cannula is advanced for its entire length into the iliac artery. The wires are removed and the extremities of the cannulas are clamped. The lines are de-aired and connected to the ECMO circuit. Finally the cannulas are secured to the skin with sutures. The mean cannulation time is around 30 min in our series with a learning curve that determined a reduction of the time from 46 min for the first 5 patients in 2008 to 29 min for the last 15 patients in 2012. If the procedure is nonemergent, a distal perfusion catheter, or at least the guidewire, is positioned in the superficial femoral artery before the insertion of the arterial cannula. *Distal perfusion* of the leg is a simple and well-accepted method to increase the circulation of the cannulated leg, and several criteria to detect leg ischemia were developed [44–49]. In an elective VA ECMO procedure, the distal perfusion catheter is inserted before arterial ECMO cannula placement, since residual pulsation of the distal artery allows its easier location. In an emergent situation, like during CPR, there is no time to insert the distal perfusion catheter electively and the maneuver is deferred starting a strict control of the limb perfusion. In our experience a distal perfusion catheter to prevent leg ischemia is placed when a *Doppler examination* of the arteries of the leg does not detect the presence of an adequate flow downstream of the arterial cannula. We choose a 6–8 F 11 cm introducer, (Avanti+, Cordis, LJ Roden, Netherlands) as the distal perfusion catheter. This can be placed percutaneously under US guidance and connected via suitable connectors to the arterial limb of the ECMO circuit.

4.7 Explantation Technique (VA and VV)

Explantation of the cannulas is performed in a standardized procedure at the bedside. If an arterial cannula is in place, heparin infusion is withdrawn and coagulation assessed to ensure the return to baseline values; in the case of VV ECMO, heparin can be

reduced, but there is no need to have a perfectly normal coagulation before deconnection. After the placement of a purse-string suture around the insertion sites, the cannulas are removed allowing a small leakage of blood to clear small thrombi from the distal portion of the leg involved. The venous site is manually compressed for 10 min, and then a slightly compressive medication is applied on cannulation site. On the arterial side, after 30–45 min of manual compression, a femoral compression system (Safeguard 24 cm. Maquet, Hirrlingen, Germany) is applied to ensure a pneumatic compression over the vessel puncture to induce hemostasis. Some ECMO centers advocate the open repair of the artery also if it was percutaneously cannulated. Strict control of the groin is implemented to recognize the development of hematoma.

A follow-up vascular ultrasound of the involved vessel is recommended; the possibility of a retained fibrin sleeve after cannula removal [50] is described and can modify the anticoagulation requirements of the patient after ECMO decannulation.

4.8 Complications of ECMO Percutaneous Cannulation

Different complications can ensue with the cannulation of the vessel for ECMO.

Early complications are directly related to the implantation procedure. Guidewire kinking, losing the vessel after full dilatation is achieved, vascular tears, not being able to advance the guidewire to the correct position due to anomalous bifurcation of the vessel, intimal dissection, and perforation are described.

Right ventricular rupture with cardiac tamponade [51] and myocardial infarction [52] are reported as complications with the insertion of the double-lumen cannula.

Bleeding from cannulation sites is still the most common complication reported in the literature [53]; with its occurrence techniques to improve vascular site hemostasis are implemented [54].

Ischemic alteration of the leg distal to arterial cannula is well described in VA ECMO, and a reperfusion cannula can be inserted electively to reduce the risk of limb ischemia. Strict monitoring of perfusion also in the venous side must be performed because a compartment syndrome can develop if the venous drainage from the distal leg is impaired by the big drainage cannula and edema develops due to a shock state. The frequency of short-term complications, including *groin hematoma*, *pseudoaneurysm*, *artero-venous fistulae*, and acute thromboembolism, varies between 2 % in VV ECMO and 8 % in VA ECMO,

Late complications affect around 12 % of VA ECMO patients and are mainly due to stenosis of the femoral artery at the former cannulation site, in particular with the surgical approach. Limb compartment syndrome occurs in about 1 % of VA ECMO patients and represents a very severe complication that can lead to amputation if not promptly recognized and treated [55, 56].

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Surgical Cannulation: Indication, Technique, and Complications

5

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5.1 Introduction

5.1.1 Surgical Methods and Vascular Access: The Decision-Making Process

In the modern era of extracorporeal life support, ECMO has been increasingly applied in several situations such as cardiac emergencies, cardiac surgery complications, or respiratory failure. The establishment of ECMO support could be achieved through intrathoracic or extrathoracic percutaneous or surgical cannulation strategies. The best cannulation technique should be chosen on the basis of patients and the clinical settings. First, it is necessary to define needs and goals of the ECMO and review the access options for the specific support and clinical setting. Such a decision process will lead the medical team to choose between a veno-venous and veno-arterial extracorporeal circulation and between a central and peripheral cannulation. The following step requires a rapid assessment of benefits and risks of the selected options to pick the best site and strategy of the cannulation. In case of central cannulation, the surgical approach through a sternotomy is required. As far as peripheral cannulation, it is necessary to choose among several sites: femoral vessels, axillary vessels, and cervical vessels are the most used ones. The cannulation could be achieved through a percutaneous, a semi-open, or a surgical approach. In the end, it is necessary to foresee and prevent complications of every chosen strategy.

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5.1.2 Open Versus Percutaneous Cannulation: When Surgical Approach Is Recommended

Peripheral vessel cannulation could be achieved either by percutaneous procedures or surgical incisions through an open approach, a semi-Seldinger, or a full Seldinger method. The open approach allows the visualization of the vessels to guarantee their adequate size, direct placement of a purse-string suture on the chosen vessel, confirmation of proper cannula placement, and good hemostasis. In addition, the vessels can be assessed for atherosclerosis, calcific disease, aneurysmal disease, and thrombosis, allowing to choose an alternative cannulation site. Furthermore, the surgeon has the option to anastomose a polytetrafluoroethylene (PTFE) or Dacron graft to obtain a safer and more efficacious cannulation with lower arterial line pressures and lower chance of malperfusion of the distal limb. The semi-Seldinger technique has the advantage of guidewires and dilators with no need of surgical arteriotomy or venotomy; at the same time it allows the assessment of the vessels, the placement of purse-string sutures, and a better hemostasis through a small incision. It is particularly attractive because it has the main features of the open cannulation and the Seldinger methodology, though it maintains a minimally invasive approach. For the venous cannulation, an entirely percutaneous Seldinger approach is generally possible. Axillary vessels represent an exception because they always need an open access. However, peripheral cannulation might be difficult during external cardiac massage or emergencies; so if arterial or venous percutaneous access fails or leads to complications, it is recommended to surgically expose the vessels and cannulate them in an open or semi-Seldinger approach. Moreover, in cases of surgical emergencies, where the peripheral vessels are already exposed, the vessels might be considered for an open or semi-Seldinger cannulation. In addition, if a vascular disease is suspected, the open evaluation of the vessels is advised.

5.1.3 Peripheral Versus Central Cannulation: Differences in Blood Flow and Mixed Cannulations

ECMO cannulation could be undertaken through peripheral vessel cannulation or central cannulation where the ascending aorta and right atrium are directly cannulated. Such an approach allows a better drainage and flow because of the use of a cannula with a larger diameter, that is why it is recommended in patients with a larger body surface area ($>2.0\text{ m}^2$). The other advantage of central cannulation is that it provides anterograde flow to the arch vessels, coronaries, and the total body. On the other hand, the peripheral cannulation on femoral vessels provides a retrograde aortic flow that blends in the arch with the blood that comes from the heart. During central cannulation, if there is no native lung function, this mixing

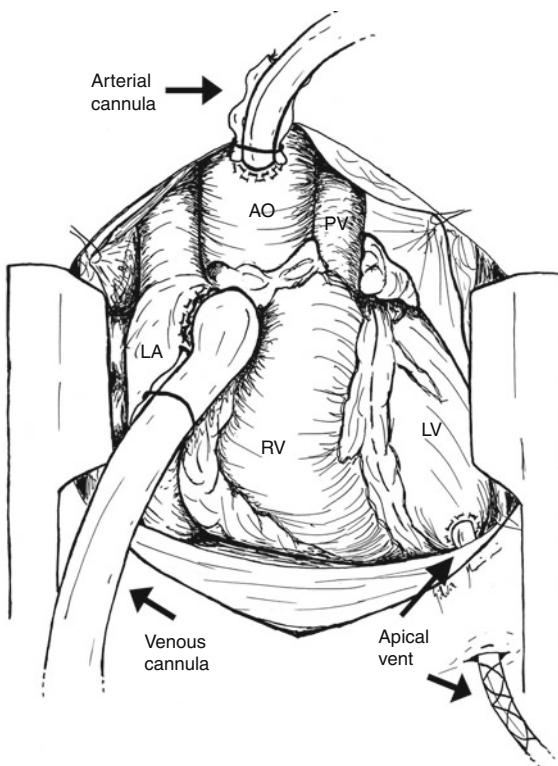
results in PCO₂ 40.5, PO₂ 100, and sat 98 %. Throughout severe respiratory failures, the blood out of the heart is desaturated and perfuses the aortic arch and coronaries. On the other hand, the saturated inflow blood perfuses the lower 2/3 of the body [1]. This is the reason why the monitoring of oxygenation from a right radial arterial line would be highly suggested. Moreover, such a slow flow in the ascending aorta could lead to clot development in the aortic root, especially if the heart is not pumping or if it is pumping only a small amount of blood. Cannulation on axillary artery or cervical vessels might provide anterograde flow with the advantages of a central cannulation and a peripheral approach. A mixed cannulation approach is possible. The medical team could choose to put both a peripheral cannula and a central one if needed.

5.2 Central Cannulation

5.2.1 Indications

Central cannulation for ECMO could be achieved through intrathoracic cannulation of the right atrium and the ascending aorta (Fig. 5.1). Such an approach requires an accurate surgical field, an open-chest procedure, a sternotomy and a surgical preparation of cannulation sites. The features listed above make the central cannulation the best approach as far as cases that require intraoperative support because of cardiopulmonary bypass wean failure. During open-chest cardiac surgery, central cannulation is often already set up, and the switch from cardiopulmonary bypass to ECMO with central cannulation is an easy and safe procedure. In addition, during the early postoperative period, chest cannulation after re-thoracotomy could ensure a rapid start of cardiopulmonary support, especially in patients who show with cardiac arrest, cardiogenic shock, or emergent chest reexploration in the intensive care unit. Central cannulation could be helpful in patients with severe peripheral disease requiring temporary circulatory support too. If no peripheral percutaneous or surgical cannulation could be obtained, an open-chest approach might be considered as well. Peripheral ECMO could be switched to central ECMO when insufficient left ventricular unloading, insufficient blood flow, or peripheral complications are detected. The central cannulation offers an optimal arterial anterograde flow and the opportunity to use cannulas with larger internal diameters so as to obtain a lower blood flow resistance and a better venous drainage. The choice of cannula size is based on the patient's body surface area and the expected blood flow. The arterial cannula usually has a 20–22-Fr diameter, whereas the venous one is often a 50–52-Fr cannula. The single-stage venous cannula is preferred to a cavo-atrial venous one because it avoids ulcers and injuries to the inferior vena cava whenever ECMO is maintained for several days. Bicaval cannulation does not have any indication in ECMO patients.

Fig. 5.1 Central cannulation.
Ao aorta, *PV* pulmonary vein,
LA left atrium, *RV* right
 ventricle, *LV* left ventricle



5.2.2 Surgical Technique

The site for the cannulation of the aorta is proximal to the origin of the innominate artery on the anterior aortic surface (Fig. 5.1). Two purse-string sutures are placed, a stab wound is made within the sutures, and the cannula is then placed in the distal ascending aorta. The two purse-string sutures are secured through two tourniquets that will be kept in the patient's thorax until decannulation (Fig. 5.2). The cannula tip must be completely within the lumen and positioned in order to direct the flow to the mid transverse aorta. It is suggested to place the cannula in an area where the atherosclerotic disease is minimal or absent.

The venous cannula is introduced through the right atrial appendage so as to allow its tip to rest in the mid-right atrium (Fig. 5.1). Before the cannula placement, a single purse-string suture is positioned, the right atrial appendage is opened, and the cannula is then inserted. Again, the suture is secured with a tourniquet. During venous cannulation, the surgeon should be careful about displacement or damage of central venous or pulmonary arterial monitoring catheters; conversely, catheters could compromise the function of venous cannula.

If an ECMO support is required after a case of difficult weaning from cardiopulmonary bypass, arterial and venous cannulas are already placed. The surgeon should

Fig. 5.2 Central cannulation: the arterial cannula. The two purse-string sutures are secured through two tourniquets that will be kept in the patient's thorax

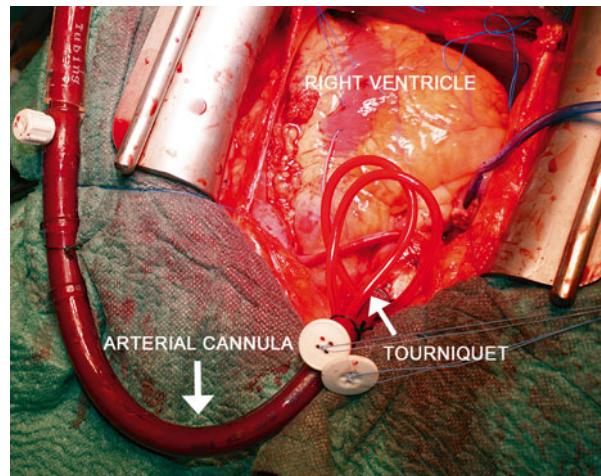
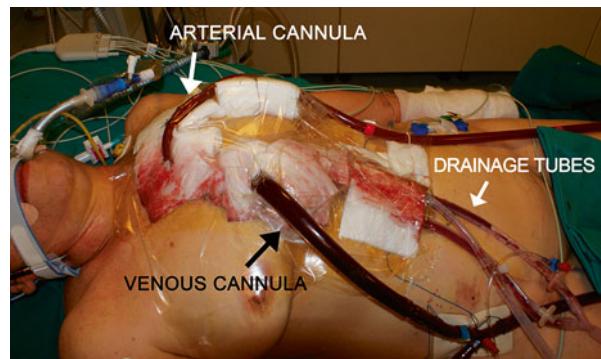


Fig. 5.3 Central cannulation. An occlusive dressing is applied to the anterior chest wall to guarantee the protection of the mediastinic structures



maintain the cardiopulmonary bypass cannulas, but he should change the circuit. First, it is necessary to stop the extracorporeal circulation, and after that to clamp the cannulas, disconnect them from the cardiopulmonary bypass circuit, connect them to the ECMO circuit, remove the clamps from cannulas, and start the new extracorporeal support.

In the end, the surgeon could introduce an apical or pulmonary vent (Fig. 5.1) to unload the left ventricle and could insert a left atrial pressure monitoring line through the right superior pulmonary vein.

At the end of a cardiac surgery intervention, after an accurate hemostasis of the heart and other tissues, mediastinal and pleural drainage tubes are positioned and the sternum is usually closed. In patients undergoing ECMO support, chest closure is not always possible. In most of such cases, it might happen that the sternum could not be closed because of the depressed cardiac function and the presence of the cannulas. When the sternum, subcutaneous tissue, and skin are left unsutured, an occlusive dressing is applied to the anterior chest wall (Fig. 5.3). Whenever possible, the skin can be sutured with Donati stitches, or a sheet of artificial tissue can be sutured

to the skin edges so as to protect mediastinal tissues and prevent infections. However, new cannulas have been designed so as to be tunneled to the subcostal abdominal wall allowing the chest to be completely closed [2].

When decannulation is required, the patient is conducted to the operating room where the chest will be opened again. The cannulas are removed while the purse-string sutures are tied with a hemostatic effect. Primary chest closure is determined at the discretion of the surgeon.

5.2.3 Perioperative Management

The proper position of the cannula is essential to provide an adequate ECMO blood flow. After central cannulation, intraoperative transesophageal echocardiography is the first technique used to confirm appropriate cannula positions and ventricular decompression before chest closure. During postoperative days, routine chest radiograph could be used to detect any change in the positions of the cannulas.

Nursing care for patients with ECMO central cannulation is more complex than the one that deals with peripherally cannulated patients. A special care must be provided to the chest dressing and cannula handling. Chest drainage tubes must be monitored very often. Every change of the position of the patient must be carefully accomplished, and patient's transport is more difficult than peripherally cannulated patients.

5.2.4 Complications and Disadvantages

Despite the advantages of the central cannulation, it is though related to important complications during cannulation and postoperative period. Major complications of ascending aorta cannulation include injury or dissection of the aortic anterior and posterior wall; misplacement of the cannula tip against the aortic wall, towards the valve, or in an arch vessel; emboli; and inadequate or excessive cerebral flow. Otherwise, venous atrial cannulation is associated to atrial arrhythmias, atrial or caval tears and bleeding, and air embolization. Local complications that may occur during and after decannulation also include bleeding, atrial or aortic injuries, and pseudoaneurysm.

Limb ischemia is generally associated to peripheral cannulation, but it can also be observed with the central cannulation. In such a situation, peripheral ischemia is no local complication but more likely an embolic phenomenon associated with the presence of aortic atheromas.

The main drawbacks of central cannulation are the open chest and the high risk of bleeding. Patients with central cannulation, compared to patients with peripheral cannulation, had a 6-fold higher rate of reoperation and a 3-fold higher rate of bleeding from cannulation sites [3]. Such conditions can be explained because the cannulas are inserted into a constantly moving organ, and the patients had a sternotomy with large areas of raw tissue. The need for repeated operations and the

evacuation of bleeding with the central cannulation contribute to the increase in terms of costs and risks for the patient [3]. Mediastinitis is more frequent in central cannulation because of the difficult management of the open chest. Moreover, patients with central cannulation could not be extubated; transports and nursing care are more difficult as already reported.

5.3 Peripheral Cannulation

5.3.1 Indications

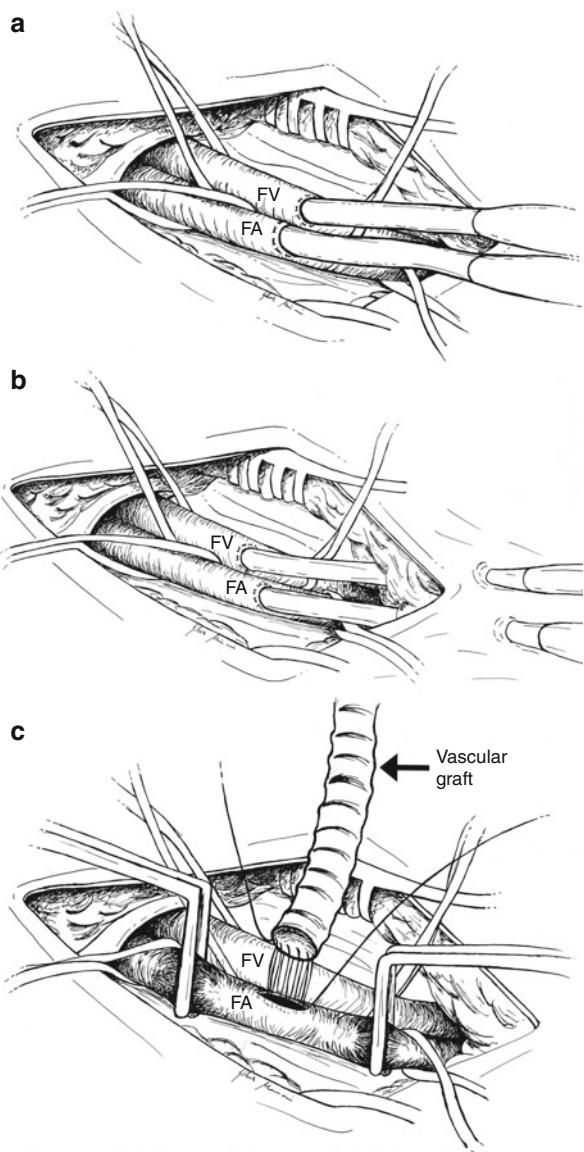
ECMO is a well-established treatment also when cardiac surgery is not involved. Peripheral cannulation does not require an open-chest approach so it results in a quicker procedure. It is useful if immediate support is needed and if ECMO is started in different hospital situations. It is recommended in case of primary cardiogenic shock, acute myocardial infarction, cardiopulmonary arrest, high-risk PTCA, myocarditis and cardiomyopathy, pulmonary hypertension, intractable arrhythmias, and respiratory failure. Moreover, peripheral cannulation allows easier nursing cares and easier and safer transports of the patients, and the patients can be extubated even if ECMO support is still ongoing. The cervical vessels and the brachiocephalic artery are the best peripheral cannulation sites in neonates and children weighing less than 15 kg. Groin cannulation of the common femoral artery and vein often provides efficient venous drainage and perfusion for larger children and adults. The axillary and iliac arteries represent additional sites that could be used.

5.3.2 Femoral Vessels

5.3.2.1 Femoral Artery: Surgical Technique

Femoral artery cannulation is probably the most common approach for ECMO implantation because of its ease and the large diameters of this vessel. Femoral cutdown is the traditional surgical approach (Fig. 5.4a). A transverse or longitudinal skin incision is made over the femoral vessels and below the inguinal ligament. Dissection is undertaken so as to isolate the femoral artery and vein, proximal and distal control of each vessel is obtained through loops, and a purse-string suture is placed. After heparinization, the common femoral artery is clamped proximally and distally, and a transverse arteriotomy is made, leaving the posterior one third of the artery intact. A 15–21-Fr arterial cannula is directly inserted. Some authors prefer the use of an 8–10-mm PTFE or Dacron “chimney graft” sewn in an end-to-side way on the arterial vessel [4] (Fig. 5.4c). Afterwards, the chimney graft can be tunneled under the skin or extended over it; the cannula is then inserted and the wound is closed. The cannula position must be fixed to the skin with multiple ligatures. Such a technique is recommended in patients with small vessels likely to be occluded by arterial cannulas (children, thin adults, peripheral artery disease), patients in whom ischemia develops after percutaneous cannulation, or patients who undergo

Fig. 5.4 Femoral vessel surgical cannulation. (a) Direct cannulation of the femoral vessels after surgical isolation of the vessels. (b) Semi-Seldinger technique: the cannulas are introduced via a separate stab incision 2 cm distal to the main incision. (c) Chimney graft technique: a PTFE or Dacron vascular graft is sewn in an end-to-side way on the femoral artery. FA femoral artery, FV femoral vein



cannulation in the operating room with vessels already exposed for CPB [5, 6]. The technique lowers the risk of distal leg ischemia and vessel dissection and simplifies decannulation. Unfortunately, this approach requires a longer preparation time, and it cannot be used in case of emergency. In such a situation, a pre-sealed short vascular prosthesis can be bevelled at its distal end and passed over the cannula. The cannula is then inserted into the vessel, and when ECMO is stable the vascular prosthesis around the cannula is lowered onto the femoral artery. In this moment, the prosthesis is anastomosed to the artery, and the arterial cannula can be

withdrawn carefully, positioning its distal end within the prosthesis at the level of the anastomosis [7]. In the semi-Seldinger technique (Fig. 5.4b), a small transverse incision is made over the femoral artery and deepened so as to expose a short length of the common femoral artery. The arterial puncture needle is introduced via a separate stab incision 2 cm distal to the incision, and it is inserted into the artery under direct vision. The following steps are the same as described for Seldinger technique. A purse-string suture on the artery could be used to assure hemostasis, and the wound is then closed. This method of insertion allows the arterial cannula to lie nearly parallel to the artery and prevents over-angulation and kinking at the entry site.

After weaning from bypass, the operative field is opened again. The cannulas are removed and the cannulation sutures tied; running or interrupted sutures are placed as appropriate. To ensure peripheral perfusion, the arterial vessel is palpated distal to the former cannulation site immediately after decannulation. In case of distal malperfusion or pulselessness, reconstructive procedures are performed. If a chimney graft is present, after the cannula removal, the side graft can be closed with staples or a snare about 1 cm above the anastomosis and the residual part can be cut. If ECMO is still necessary, a new graft may be sutured to the stump of the old graft [4]. In cases of percutaneous cannulation, some authors suggest an open repair of the vessel in order to prevent bleeding and hematoma development [8]. Open repair of vessels also allows evaluation for potential areas of stenosis and ability to perform patch angioplasty if needed [8].

5.3.2.2 Femoral Vein: Surgical Technique

Femoral vein cannulation is more often percutaneously performed. Surgical isolation is performed when percutaneous approach fails or if femoral vessels are already exposed. Some authors suggest the cannulation of right femoral vein because of the easier placement of the cannula up to the right atrium, due to the relationship of the iliac vein and inferior vena cava to the iliac crest [9]. Some others suggest the cannulation of the contralateral femoral vein as opposite to the cannulated femoral artery to avoid a cluttered field [10]. The skin incision and the dissection techniques are the same as described above. Venous cannulation is performed first. A circumferential purse-string suture is placed in the anterior wall of the vein; the common femoral vein is then clamped proximally and distally. A venotomy is made within the purse string, the venous cannula is inserted, and the proximal and distal clamps are removed. The cannula is finally advanced up to the right atrium. Once properly positioned, the venous cannula is fixed, the arterial cannulation is performed, and the wound is closed. Cannula diameter size is from 19 to 25 Fr.

5.3.2.3 Limb Ischemia and Distal Perfusion: Open Access

Ischemic complications using different approaches for femoral cannulation varied between 10 and 70 % [11]. Peripheral arterial disease is an independent predictor of vascular complications, and assessment of ankle–brachial index before ECMO implantation is recommended whenever possible [11]. During ECMO support a nursing protocol for early detection of vascular complication is suggested. Bisdas

et al. [11] established the following protocol: (1) clinical examination of feet and legs for temperature, color, capillarity, and compartment syndrome and, additionally, continuous measurement of oxygen saturation of toe and comparison with the respective finger; (2) Doppler detection of peripheral pulses/arterial blood flow by an experienced physician every 6 h; (3) measurement of myoglobin and creatine kinase every 8 h; and (4) if items 1–3 reveal any problems, color Duplex ultrasonography is used, or in case of inconsistent results, contrast-enhanced computed tomography angiography. The same protocol is followed during the first 48 h after ECMO explantation. Therefore, distal limb perfusion is critical, and many authors recommend its implantation at the time of ECMO start or following specific criteria. Huang et al. [12] measured the mean arterial pressure of the superficial femoral artery by puncturing the vessel distal to the ECMO cannula with a 23-gauge needle. If the pressure was under 50 mmHg, a distal perfusion cannula was recommended. Similarly, a larger cannula size-to-BSA ratio could predict which patients could develop ischemia [13]. Surgical approach to solve such a problem may interest the femoral artery, the tibial artery, or the dorsalis pedis artery. If the femoral vessels are already isolated, the chimney graft anastomosed to the femoral artery could guarantee the distal perfusion of the leg. Otherwise, a cannula can be placed in the distal femoral artery or in the superficial femoral artery with the same technique described before [14–16].

When a severe atherosclerotic lesion or anatomical problems affect the distal common femoral artery or the superficial femoral artery, distal perfusion through the posterior tibial artery and the dorsalis pedis artery may be an effective alternative treatment. For the posterior tibial cannulation, a longitudinal incision of 5 cm in length is made just posterior to the medial malleolus. The fibrous flexor retinaculum is divided, and a small self-retaining retractor is inserted. The posterior tibial artery is easily identified by its venae comitantes, and it is circumferentially isolated. The tibial nerve is preserved. The artery is ligated distally and a small arteriotomy is created. A cannula is then inserted in a retrograde direction [17]. For the dorsalis pedis artery cannulation, a small incision is made on the dorsal portion of the foot. After isolation of the deep peroneal nerve, the artery is isolated and cut down and the distal side is ligated. An intravascular catheter is inserted into the artery, and, after the catheter is connected to the tubing of the arterial branch of the circuit, blood flow to the dorsalis pedis artery is initiated [18].

Another potential complication of femoral cannulation is venous congestion of the leg by the venous cannula [19]. Superficial femoral vein could be cannulated percutaneously or through a surgical approach if femoral vessels are already exposed [14].

5.3.2.4 Complications

The main complication of femoral vessel cannulation is distal limb ischaemia and reperfusion injury even leading to limb amputation. However, other morbidities include pseudoaneurysm, neurological injury and femoral nerve weakness, compartment syndrome, retrograde arterial dissection, arterial and venous laceration or perforation, arterial thrombosis and deep vein thrombosis, embolization of luminal

debris, arteriovenous fistula, and wound complications such as lymphocele, infection, and hematoma [20, 21]. Femoral cannulation site wound healing could be problematic in the immunocompromised, malnourished, vasculopathic, obese, or diabetic patients [22]. Common femoral vein cannulation could be complicated by an inability to negotiate the cannula successfully across its long course to the right atrium, pelvic venous injury, and retroperitoneal bleeding. It is also contraindicated in the presence of an inferior vena cava filter, deep venous thrombosis, or other intrinsic or extrinsic obstruction to the pelvic veins or inferior vena cava [22]. Cannula displacement or dislocation is possible during handling of the cannulas. Transesophageal echocardiography and routine chest radiograph could be used to detect any change in the positions of the cannulas. Anti-infective and graft anastomosis management should include a sterile, graft-covering dressing with daily monitoring and skin disinfections with chlorhexidine every 2 days, concomitant antibiotic therapy extended to day 3 after graft closure and minimization of hip flexion [5, 23]. The monitoring of the surgical wounds and interested limbs should be extended to days that follow the decannulation so as to verify if a surgical reexploration is needed.

5.3.3 Axillary Vessels

5.3.3.1 Indications

Even if femoral vessels are the first choice for peripheral cannulation, different sites could be considered. The use of the right axillary artery as inflow in the ECMO circuit has several potential advantages:

- It provides an antegrade flow and excellent upper body oxygenation.
- It is easy and reproducible.
- It is a safe procedure with low complication rates.
- It may avoid cerebral embolization, and this artery is usually free from arteriosclerotic disease.
- It allows closure of the chest after postcardiotomy shock and an easy decannulation [24].
- It has a lower rate of complications of arm ischemia because the axillary artery benefits from rich collateral flow from the thyrocervical trunk to the suprascapular and transverse cervical arteries [25].

Therefore, axillary cannulation could turn to an option for the following: postcardiotomy patients, patients presenting with an important peripheral vascular disease (aortoiliac aneurysms, severe peripheral aortoiliac occlusive disease, or arteriosclerosis of the femoral vessels), patients with limb complications related to femoral artery cannulation, and patients under peripheral ECMO support with inadequate upper body oxygenation and perfusion [24]. Such an approach is contraindicated if there is an extension of an aortic disease into the artery or a known axillary/subclavian stenosis or atheroma. Obesity and wall chest edema is a relative contraindication as the exposure of the artery could be difficult. The major disadvantage of the axillary cannulation is that it is not available for emergency and it cannot be percutaneously performed.

5.3.3.2 Axillary Artery: Surgical Technique

There are quite a few incision techniques in order to expose the right axillary artery. Several authors [26] prefer an 8–10-cm horizontal incision below the medial third of the clavicle, because of a lower risk of brachial plexus injury. Some others [24] prefer the deltoideo-pectoral approach with a 6–10-cm incision below and parallel to the lateral two thirds of the clavicle. The pectoralis muscle is then divided parallel to its fibers; the clavipectoralis fascia is incised, exposing the pectoralis minor, which is divided or retracted laterally. The axillary artery is identified superior to the vein and by palpation. The brachial plexus is carefully dissected from the artery. Proximal and distal control of the artery is obtained through loops. If the artery is good sized and with a good exposure, direct cannulation could be performed. A single purse-string suture is placed in the anterior wall of the axillary artery, and, after heparinization, the artery is clamped and the cannula is inserted. In patients with a small body surface area and small vessels, an 8-mm Dacron side graft is best (Fig. 5.5a). The chimney graft can be extended over the skin (Fig. 5.5 B1) or tunneled under it and exteriorized by a small second

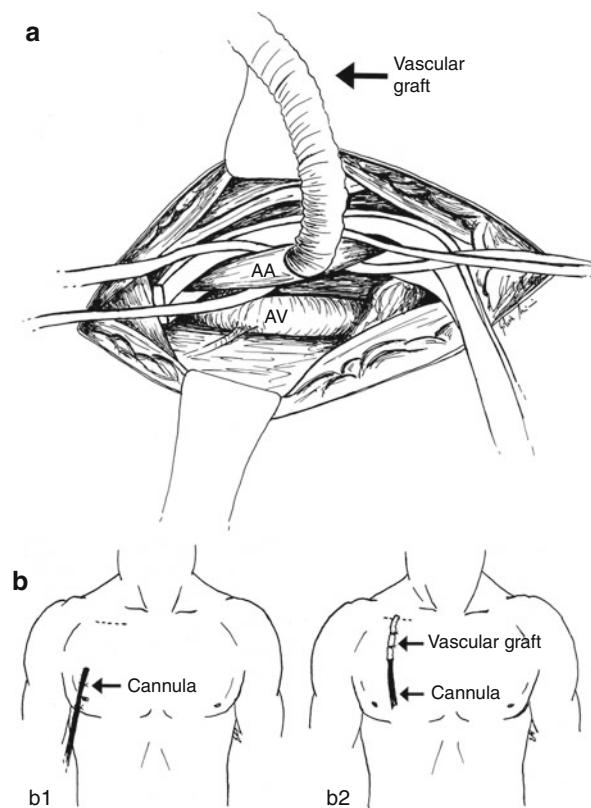


Fig. 5.5 Axillary vessel surgical cannulation. (a) Side-graft cannulation technique: an 8-mm Dacron side graft is sewn in an end-to-side way on the axillary artery. The arterial cannula is then inserted into the vascular graft. (b) The chimney graft can be tunneled under the skin (B1) or extended over it (B2). AA axillary artery, AV axillary vein

incision (Fig. 5.5 B2). The cannula is then connected to the distal graft. After accurate hemostasis, the wound is closed. After weaning from ECMO, the surgical field is revised and the axillary artery is repaired. In case of direct cannulation, the axillary artery is directly repaired. When the primary closure narrows the artery, a patch is recommended [27]. If a side graft is used, it could be closed as described above.

5.3.3.3 Axillary Vein: Surgical Technique

Axillary vein cannulation is rare in ECMO patients. Axillary vein lies superficial to the artery, and it is easily accessible when the arterial cannula is already placed. A purse-string suture is made at the cephalic vein–axillary vein junction. The mobilized segment of the vein is clamped distally, and a longitudinal venotomy is performed within the purse string. The cannula is later introduced.

5.3.3.4 Complications

Even if limb ischemia and compartment syndrome could be avoided with axillary cannulation, other complications could occur with such a technique. Hyperperfusion syndrome occurs in nearly 20 % of the patients, and it is more frequent with the use of a side graft [28]. This syndrome could develop because of an arterial outflow obstruction. That occurs in case of technical problems in the construction of the side graft that could narrow the artery and cause a preferential flow down the arm. A similar pattern could be expected with atherosclerotic aortic arch disease and/or acute type A dissections. Venous obstructive causes could include bleeding, a compressive hematoma, and the presence of a venous cannula or deep vein thrombus. The management of hyperperfusion syndrome is directed to solve its etiology [28]. Other further complications are stump graft and wound infection, stroke, brachial plexus injury, and axillary artery injury or dissection due to its fragility whenever directly cannulated.

5.3.4 Cervical Vessels

5.3.4.1 Indications and Complications

Cervical cannulation is widely used for ECMO in neonates and infants, and it is rarely used in adults. The only exception occurs as far as the right internal jugular vein that is often cannulated in veno-venous ECMO and to increase venous drainage in venoarterial ECMO. Percutaneous cannulation of the jugular vein is the most used cannulation technique even if the semi-Seldinger technique and the open technique are possible alternative solutions when the percutaneous approach is not feasible. Carotid artery cannulation is frequently related to cerebrovascular accidents, and that is why it is usually avoided in adult ECMO cannulation. Right internal jugular vein could be related to neurologic complications that may result from intraventricular hemorrhage, cerebral edema, or hypoxia. Local complications are vagus nerve injuries, arterial dissection, arterial and venous laceration or perforation, thrombosis, infection, bleeding, and hematoma.

5.3.4.2 Surgical Technique

The surgical technique that is often used to cannulate the right internal jugular vein is the semi-Seldinger. The patient is placed supine while the head is turned to the left. The right internal jugular vein is exposed through a transverse incision over the lower third of the sternocleidomastoid muscle. The vein is dissected and proximal and distal control is obtained. A small stab incision is made cephalad to the main incision, and, after heparinization, the introducer needle is passed through the stab into the vein. Exposure of the vein allows to size the cannula and to monitor any injury during cannulation. The guidewire is passed through the needle, and the following steps are the same as described for Seldinger technique. The cannula tip is placed into the right atrium. This approach does not require any ligation of the vein, and it facilitates the process of decannulation. The absence of ligation of the right internal jugular vein allows drainage of deoxygenated blood down the ipsilateral vessel and into the cannula. Such a practice reduces recirculation and could also have an impact on the intracranial venous pressure and the incidence of intracranial hemorrhage [10].

The open approach is recommended when the cannulation of the carotid artery is required. The vessels are exposed as described previously. The internal jugular and carotid artery are isolated and controlled. A careful attention must be paid in order to not injure the vagus nerve, which lies behind the neck vessels within the carotid sheath. After the heparinization and the arteriotomy, the cannula is inserted and fixed with the tip of the cannula placed at the orifice of the innominate artery. The venous cannula is placed in the same way [10]. In neonates, the most widely used cannulation technique employs the permanent ligation of the jugular vein and the carotid artery cephalically to the cannulation sites.

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Materials: Cannulas, Pumps, Oxygenators

Umberto Borrelli and Cristina Costa

6.1 Introduction

Over the past decade, several improvements have been made to the extracorporeal circulation (ECC) used in cardiac surgery (cardiopulmonary bypass). These include a reduction in the surface contact between blood and air, improved biocompatibility between blood and materials, and the use of compact circuits and the assisted venous drainage. These improvements have made possible to optimize other ECCs, specifically extracorporeal membrane oxygenation (ECMO) and extracorporeal life support (ECLS) [1–11], and, as such, led to the introduction to the market of specific circuits validated for several weeks of continuous use (14–30 days).

ECMO is a closed ECC circuit, without air/blood interfaces. Its internal surface is completely treated by glycoproteins or by pre-heparinization with covalent and/or ionic bondings (Fig. 6.1). These treatments lead to an improved blood compatibility, the reduction of the inflammatory response, and better patient anticoagulation [10–12].

ECMO is classified according to the connection with the blood circulation of the patient.

6.1.1 Venovenous ECMO (VV)

Used most frequently in the treatment of severe respiratory compromise, venovenous ECMO has both the inflow and outflow cannula placed in the patient's venous circulation.

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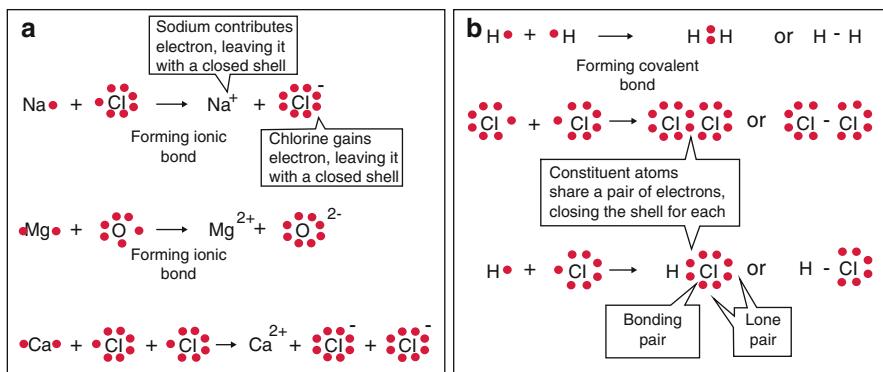


Fig. 6.1 The techniques used to coat the circuits are classified into two categories: (a) Ionic bond: bond in which one or more electrons from one atom are removed and attached to another atom, resulting in positive and negative ions which attract each other. (b) Covalent bond: bond in which one or more pairs of electrons are shared by two atoms

6.1.2 Venoarterial ECMO (VA)

Able to totally or partially bypass the lungs or heart, venoarterial ECMO allows for full cardiac or pulmonary support. It can be used to provide support of the vital organs, temporary circulatory support, and/or relief to the heart during myocardial recovery. Where appropriate, it can also be a bridging therapy to transplantation or establishment of a mechanical heart. During VA ECMO, the inflow cannula is placed in the patient's venous circulation and the outflow cannula in the arterial circulation.

6.2 Biocompatible Components

Currently, there are several approaches to improve the biocompatibility of cardio-pulmonary bypass components, based on the use of antithrombotic biomolecules such as heparin, polymeric molecules, and new glycoprotein molecules. Heparin is a negatively charged, hydrophilic, complex polysaccharide acid.

6.3 Example of Biocoating That Is Used During ECMO

- The Carmeda coating allows heparin molecules to be attached to the biomaterial surface by a covalent bonding.
- The Duraflo II heparin coating ionically attaches heparin to a quaternary ammonium carrier, which binds to the biomaterial surfaces.
- The Rheoparin coating fixes the heparin molecules to the biomaterial surface, due to ionic forces.

- The Physio coating is composed of a phosphorylcholine polymer. The heparin is not present in this type of coating and is based on a phosphorylcholine molecule.
- The Bioline coating combines polypeptides and heparin. Polypeptides are adsorbed onto the components of the CPB surface forming a steric hindering. The heparin molecules are attached to the polypeptides via triple covalent bonds and ionic interaction.

6.3.1 ECMO Circuit for Adult Patients

The ECMO circuit for an adult patient usually consists of an inflow cannula (venous cannula), a tubing made of polyvinyl chloride (PVC) with 3/8" of diameter, a centrifugal pump, a heat exchanger embedded in a membrane oxygenator made of polymethylpentene (PMP) membrane, and an outflow cannula that transports arterialized blood (arterial cannula).

The circuits are usually very compact, with some flexibility for transportation, mobilization, and general care of patients in the ICU. ECMO circuits have several sites for monitoring including pressure measurement, blood sampling, and the continuous analysis of blood parameters in the inflow (venous blood) or outflow (arterial blood) lines. It is also possible to connect a hemofiltration system or hemodialysis machine on the ECMO system, according to the operating characteristics of these devices. Some ECMO consoles may be equipped with a servo controller that allows control of the centrifugal pump rotations, in relation to the negative pressure (P^1) in the inflow line (Fig. 6.2).

The choice of the different components being a part of ECMO circuit is very important because it reduces the physiological impact of the assist system on the patient. Depending on the type of assistance to be performed, the selection of the oxygenator is a priority, because it represents the largest contact area between blood and materials in the circuit.

The geometry and the internal resistance of each component will induce a pressure drop that will influence the hemodynamics in the system, the management of the system and the evolution of the patient. The optimization of the position of the cannulas, the appropriate selection of circuit components and the use of the surface treatment (tip to tip) can reduce the impact of ECMO on the patient. This is comparable to an artificial reduction of the assistance time [3, 6, 8–18].

6.3.2 Centrifugal Blood Pumps

Centrifugal pumps are nonocclusive, and as such, there is a risk of inducing a back-flow of blood against the current through the pump. This is the reason that some consoles are equipped with anti-reflux system. ECMO dedicated centrifugal pumps are driven by electromagnetic induction motors and uses the principles of centrifugal force to generate a flow (described in terms of liters/minute), which is created by the rotation of the cones, fins, or vanes and rotors (Fig. 6.3).

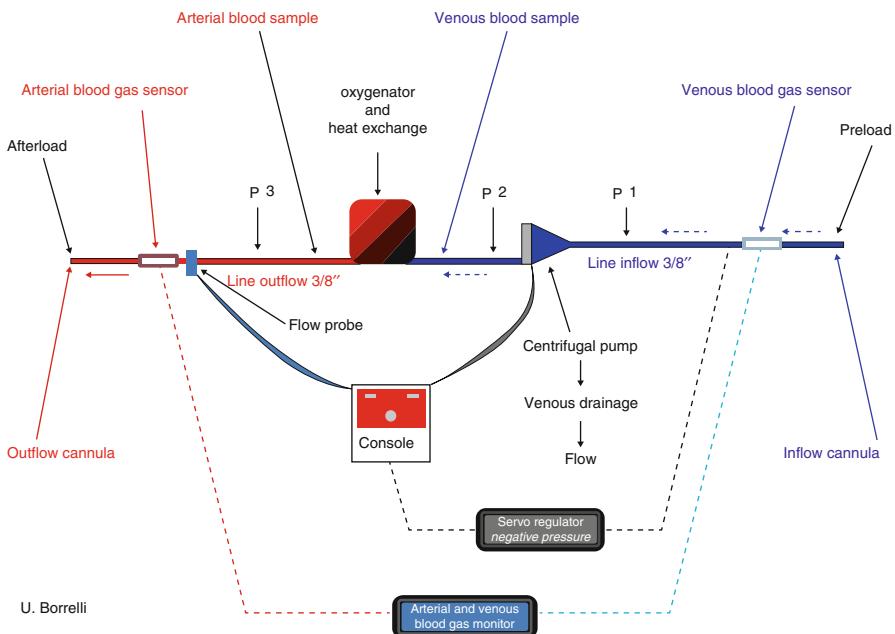


Fig. 6.2 Characteristics of the ECMO circuit for adult patients. P^1 Negative pressure suction from the inflow line, between the inflow cannula and the entrance of the centrifugal pump. P^2 Positive ejection pressure between the outlet of centrifugal pump and the inlet of the oxygenator. P^3 Positive ejection pressure of the outflow line, between the outlet of the oxygenator and the outflow cannula. $P^2 - P^3$ Corresponding to the gradient of pre- and post-oxygenator pressure, it indicates the pressure drop of the oxygenator

The flow is controlled by either electromagnetic or ultrasonic flow meter. Flow depends on the speed of rotation per minute (RPM) of the centrifugal pump, the hemodynamic conditions including the preload or afterload, and the characteristics of the inflow or outflow cannulas that are used including their positioning. To ensure adequate preload, the centrifugal pump and the oxygenator should preferably be below the level of the right atrium (RA) of the patient. An increase in the negative pressure suction upstream of the centrifugal pump (P^1) will be the result of a decrease in preload. An increase in the positive pressure ejection downstream of the oxygenator (P^3) is generated by an increase of the afterload. Both of these phenomena decrease flow despite a constant pump speed (RPM). It is important to check the parameters of the patient, the position of the cannulas, and the absence of kinking or clamping on the lines and of thrombi in the circuit.

A decrease in preload causing a significant increase in P^1 can induce the phenomena of cavitation (chattering) in the inflow line. This can cause major trauma to the blood, resulting in hemolysis, gaseous microemboli, and other adverse events. It is for this reason that some ECMO circuits use a servo controller to maintain a safe relationship between the pump speed (RPM) and P^1 . This ensures that there is time available when preload decreases to treat the cause before cavitation and its



Fig. 6.3 (a) Centrifugal pump console (SCPC) Revolution of Sorin Group. (b) SCPC Affinity CP of Medtronic. (c) SCPC CentriMag of Levitronix. (d) SCPC Cardiohelp System of Maquet. (e) SCPC Rotaflow of Maquet. (f) SCPC DeltaStream of Medos

consequences occur, thereby reducing the probability of trauma to the blood and the appearance of gaseous microemboli [9, 10, 13, 14].

Prior to stopping a centrifugal pump, it first is necessary to clamp the outflow line. Once the pump has been deactivated, the inflow line should be clamped.

6.3.3 Membrane Oxygenator

The membrane oxygenators are placed distal to the centrifugal pump. They are generally equipped with a heat exchanger made of polyurethane, polyester, or stainless steel. Depending on the model, the surface of the heat exchanger varies from 0.14 to 0.6 m² (Table 6.1).

A temperature gradient between the water and the blood enables temperature adjustment (Fig. 6.4). This area forms a thermal bridge and enables the patient to be either warmed or cooled. The oxygenator is the largest area of contact between the blood and the ECMO circuit, and its choice will depend on both patient factors and the underlying pathology being treated. Oxygenators used in cardiac surgery have a microporous membrane of hollow polypropylene (PP) fibers. They intent to replace the pulmonary alveolar function of the patient and ensure the delivery of O₂ and the removal of CO₂. The use of these oxygenators is generally limited to around 8 h.

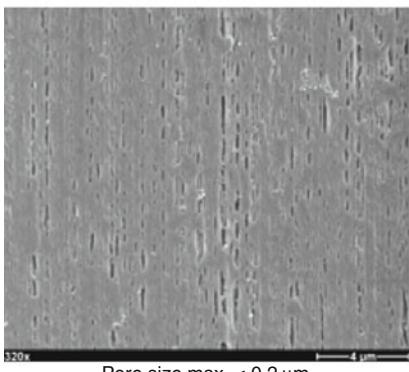
Table 6.1 Characteristics of the oxygenators

Oxygenators Specifications	Sorin EOS ECMO	Maquet Quadrox PLS	Maquet HLS module Integrated centrifugal pump	Medos Hilite 7000LT
Blood flow rate	0.5–5 l/min	0.5–7 l/min	0.5–7 l/min	0–7 l/min
Membrane surface area	1.2 m ²	1.8 m ²	1.8 m ²	1.9 m ²
Membrane type	PMP fiber	PMP fiber	PMP fiber	PMP fiber
Biomedical coating	Phosphorylcholine	Bioline	Bioline	Rheoparin
Static priming volume	150 ml	250 ml	273 ml	270 ml
Heat exchanger surface area	0.14 m ²	0.6 m ²	0.4 m ²	0.45 m ²
Heat exchanger material	Stainless steel	Polyurethane	Polyurethane	Polyester
Size of blood inlet and outlet connectors	3/8"	3/8"	3/8"	3/8"
Size of water connectors	1/2" Hansen coupling	1/2" Hansen coupling	1/2" Hansen coupling	1/2" Hansen coupling

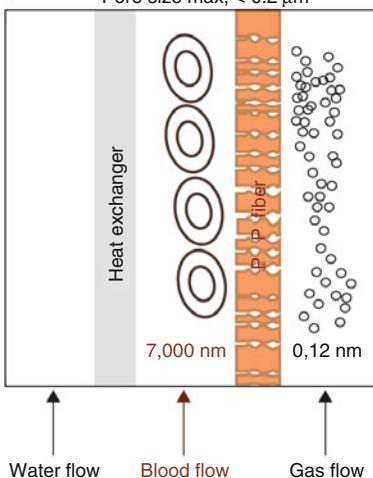
This usage limit is due to the microporous structure of the fiber, which may alterate over time, causing plasma leakage of the membrane [14]. The result is a decrease in performance of the gas fibers and/or plasma leakage situated at gas outlet of the oxygenator (gas out) (Fig. 6.5).

Different kind of membranes are used for ECMO oxygenators. Following membrane characteristics can be observed: silicone caoutchouc, selective permeability or polymethylpentene (PMP), depending on the models; the surface of the membrane varies from 1.2 to 1.9 m². The PMP membrane is made of hollow fibers. The fiber structure itself is covered with a dense but tiny outer skin, characterizing it as a diffusion membrane, avoiding plasma leakage. The gas permeability for oxygen and carbon dioxide is excellent and the gas exchange capability remains equivalent to the micro porous membranes. This is one of the reasons why the membrane remains functional during several weeks without oxygenator exchange. The gas exchanges diffuses through the membrane due to the partial pressure gradient on both sides of the membrane. There is consequently no direct gas/blood interface (Fig. 6.5). Their physical characteristics are tailored to meet the demand for gaseous and thermic exchange (Table 6.1). A gas blender mixing air and O₂ is connected to oxygenator permitting the adjustment of exchange O₂ and CO₂ selectively. Especially, the flow of the gas mixture (“the sweep”) acts to determine the extraction of CO₂ and the FiO₂ from 21 to 100 % (the oxygen concentration of the mixture) acts to govern the transfer of oxygen into the blood.

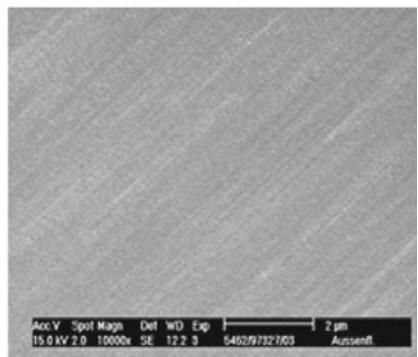
Polypropylene microporous membrane (PP)



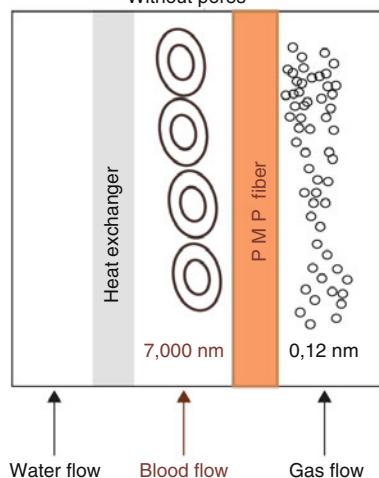
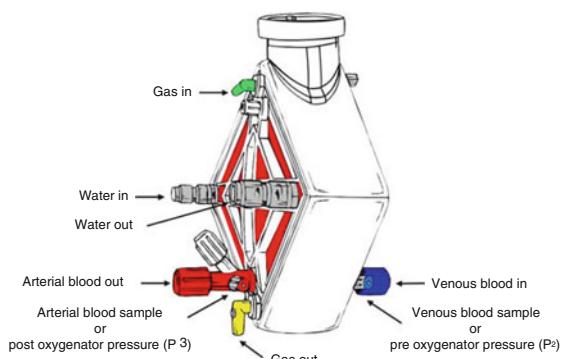
Pore size max, < 0.2 μm



Polymethylpentene membrane (PMP)



Without pores

**Fig. 6.4** Different parts of the oxygenator**Fig. 6.5** Overview of the oxygenator

The pressure drop generated in the oxygenator depends on its physical characteristics or by variation of its internal resistance during ECMO use (including blood temperature, viscosity, and thrombus formation on the membrane). It is measured by the pre- and post-oxygenator pressure gradient ($P^2 - P^3$). An increase in the pressure drop of the oxygenator may indicate deterioration of the hemodynamics of the membrane, which in turn may impair gas transfers and should prompt consideration regarding changing of the oxygenator [11, 16].

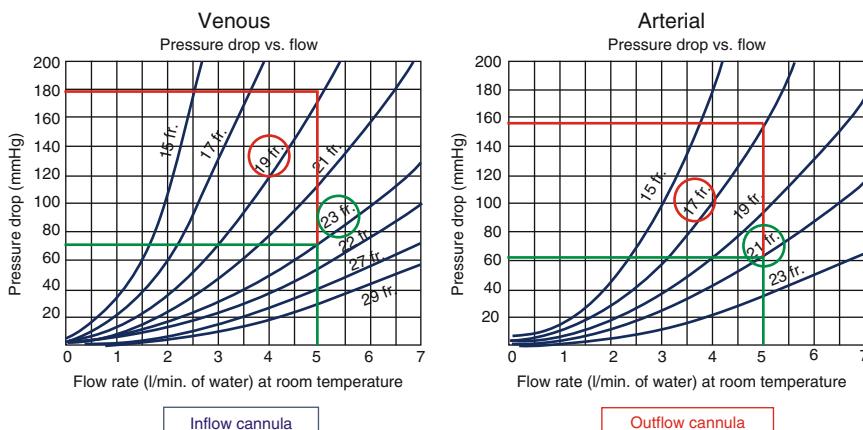
6.3.4 Cannulas for Adult Patients

The blood flow in the ECMO circuit is determined by the size of the cannula (internal diameter and length), the design, the pressure drop, and the positioning. The choice of the cannulas is made according to the mechanical and fluid characteristics (pressure, flow, etc.) (Table 6.2). It takes into account surgical needs, cannula placement (central or peripheral), the quality of the patient's blood vessels, and the type of ECMO to be used (e.g., VA or VV). Certain ECMO configurations are especially designed to suit the type of cannulation, for example, to suit the dual-lumen single cannulation of the jugular vein or the double femoro-jugular cannulation (Fig. 6.6).

The cannulas designed for circulatory assistance are designed for percutaneous access into the arteries or veins of the patient. They usually have a wire enforced body on the longest part of the cannula in order to prevent changes in their hemodynamic characteristics during the mobilization of the patient (Fig. 6.7).

Additionally, the temperature of the circulating blood in the ECMO circuit can change the resistance of the cannula. The hemodynamics of ECMO can also be affected by compression of one or more of the cannulas by intrathoracic and/or intra-abdominal pressure (cough, pleural effusion, and/or intra-abdominal hypertension).

Table 6.2 Example of pressure drop for arterial and venous cannulas



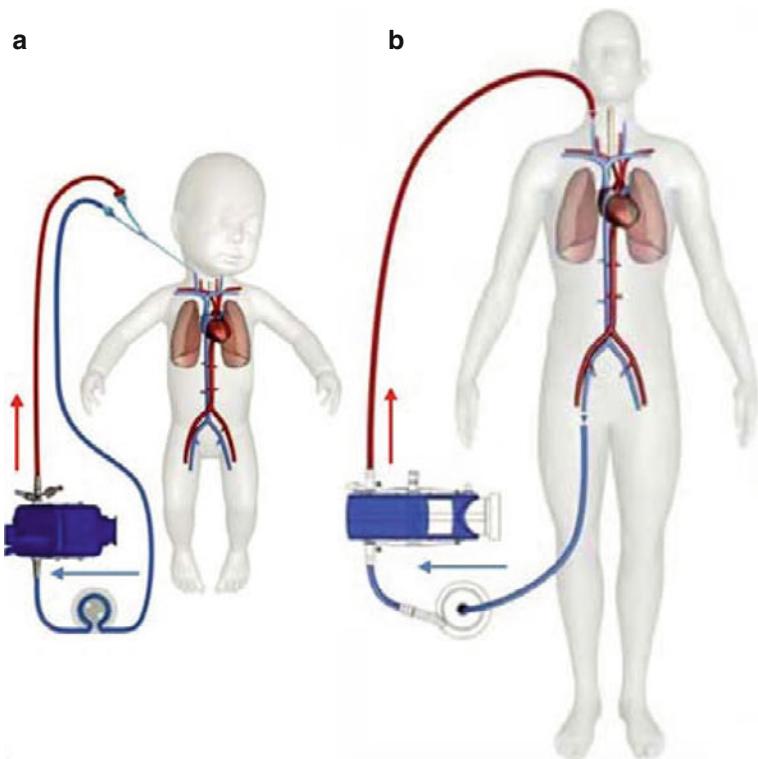


Fig. 6.6 (a) VV ECMO with a double-lumen cannula. (b) VV ECMO with two cannulas placed in the jugular and femoral veins

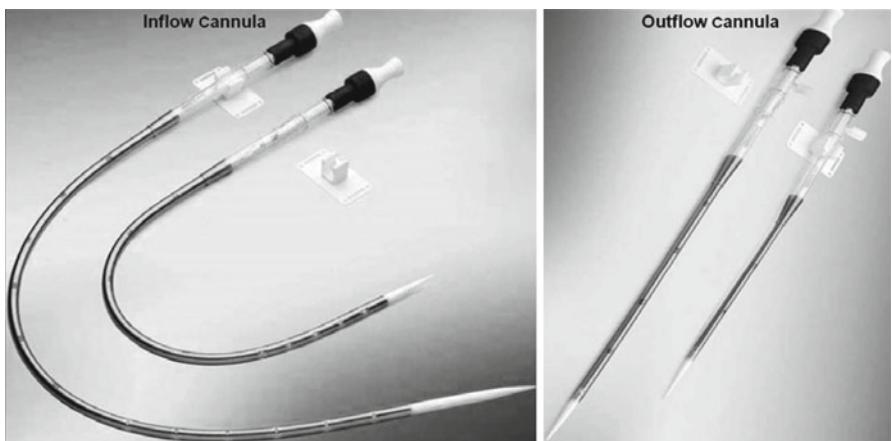


Fig. 6.7 Example of percutaneous cannulas

Logically, the use of inflow and outflow cannulas with maximal diameter would reduce the pressure drop in the circuit. However, like often in ECMO, a balance has to be found between treating the pathology and minimizing trauma and discomfort to the patient caused by the presence of the cannulas in the vascular system.

The correct selection of in- and outflow cannulas, as well as their positioning, is very important. They help to optimize the hemodynamics of ECMO in relation to the patient and ensure an adequate flow able to satisfy the physiological demands to be met. This results in a reduction in the trauma to the blood cells, thereby reducing hemolysis and gaseous microemboli [13, 14, 17], by preventing an excessive increase in the P^1 or P^3 (Fig. 6.2.).

6.3.4.1 Venous Cannulas

Venous cannulas (the inflow cannula) are longer than the outflow cannulas (± 55 cm) as they need to reach from their insertion point in the common femoral vein to adjacent to the right atrium (RA). They have a larger diameter than outflow cannulas (15–29 Fr) and a larger proportion of their length is multiperforated. These features reduce the pressure drop and limit the phenomena of chattering avoiding a significant collapse of the wall of the right atrium (RA) or the inferior vena cava (IVC). The result of these characteristics will allow the observation of a decreased pressure drop at the pressure drop at P^1 (Fig. 6.2.) by increasing the drainage flow while maintaining a constant preload and the RPM of the centrifugal pump. In certain circumstances, the cannula design allows the use of smaller inflow cannulas without causing deleterious hemodynamic consequences while maintaining the same flow (Table 6.2). During pulmonary assistance (VV) using a femoro-jugular cannulation, the inflow cannula is placed in the inferior vena cava with its distal tip at the level of the subhepatic veins, while the outflow cannula is placed via the jugular vein into the superior vena cava (SVC) with its distal tip at the level of the right atrium.

To eliminate the discomfort that is caused by the presence of the cannula in the jugular vein, or for certain therapeutic reasons, some centers cannulate the right and left femoral veins. This requires the use of two different cannulas with different design and diameters. The distal tip of the inflow cannula is positioned through the left femoral vein at the level of the subhepatic veins, while the distal tip of the outflow cannula is positioned through the right femoral vein at the level of the right atrium. This combination can reduce the effect of shunt (recirculation) between the two cannulas.

6.3.4.2 Arterial Cannulas

Arterial cannulas (outflow cannula) are smaller than venous cannulas both in terms of diameter (15–23 Fr) and overall length. They have some perforations at their distal tip, though these are not as extensive as in the venous cannulas. According to their characteristics, a pressure drop at the outflow cannula can be observed when P^3 increases (Fig. 6.2) causing a decrease in flow despite a constant afterload and RPM of the centrifugal pump. During femoro-femoral VA ECMO, the outflow cannula is placed into the common femoral artery. The particular position of the cannula can cause ischemia of the ipsilateral lower limb. This can be prevented by the introduction of a 6 fr catheter for a distal perfusion [18] connected to the Luer connector of the outflow cannula and introduced few centimeters downstream the superficial femoral artery.

The placement of the cannulas is guided by echocardiography (TEE) and/or fluoroscopy.

In general, the cannulas have a radiopaque marker, though the distal few centimeters are often radiotransparent.

6.4 Conclusions

The optimization of the various components of the ECMO and its management in relation to the pathology have a significant and direct impact on the prognosis and disease course of the patient requiring circulatory assistance.

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Coagulation, Anticoagulation, and Inflammatory Response

7

Marco Ranucci

7.1 Introduction

Extracorporeal membrane oxygenation (ECMO) represents a modified system of cardiopulmonary bypass (CPB). Depending on the type of cannulation, it may assist or replace both the cardiac and the pulmonary function (arteriovenous ECMO) or the pulmonary function alone (venovenous ECMO). Regardless of this difference, the ECMO circuit always includes a centrifugal pump, tubings, and an oxygenator. To this respect, the pathophysiological reactions of blood coming in contact with foreign surfaces are similar to those observed during CPB. However, major differences exist between CPB and ECMO, with different degrees of hemostasis and coagulation and inflammatory reactions.

As a consequence, the management of anticoagulation during ECMO strongly differs from the conventional anticoagulation regimen required by CPB.

This chapter provides an overview of the hemostatic system activation, inflammatory reaction, and anticoagulation protocols for adult patients on ECMO.

7.2 Hemostatic System Activation During ECMO

The main scientific information on hemostatic system activation derives from studies in the field of dialysis and, most importantly, CPB during cardiac operations. Conventionally, the hemostatic system activation may be triggered by material-dependent and material-independent mechanisms.

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7.2.1 Contact Phase: The Material-Dependent Blood Activation and the Role of Fibrinogen and Platelets

The extensive contact between blood and foreign surfaces triggers a material-dependent blood activation through the *contact phase*. Given the large contact surface area represented by the hollow fiber of membrane oxygenator, ECMO is a classical model of contact-phase activation.

The initial reaction of blood coming in contact with foreign surfaces, and basically with plasticizers, is based on the interaction between the surface and the plasma proteins. This produces a layer of proteins on the surface of the circuit and oxygenator, which is mainly represented by fibrinogen, albumin, and γ -globulins.

The initial layer is mainly represented by fibrinogen, through the interaction between the hydrophobic foreign surface and hydrophilic sites of fibrinogen. Once fibrinogen is bound to the surface, this will in turn trigger platelet adhesion to the fibrinogen receptors. Other blood cells like fibroblast, leukocytes, and even red cells may participate in this layer. Fibrinogen is the main determinant of the initial protein layer on the foreign surface.

Simultaneously, the coagulation system becomes activated through the so-called intrinsic pathway. Factor XII (Hageman factor) is activated to factor XIIa, leading to the subsequent activation of pre-kallikrein, high-molecular weight kininogen, and factor XI. With the subsequent contribution of factors IX and X, prothrombin (factor II) is activated to thrombin (factor IIa) [1].

The material-dependent blood activation is of course dependent on the nature of the materials. Presently, all the systems available for ECMO are equipped with biocompatible surfaces, which limit the severity of this reaction.

The most commonly used biocompatible treatments are based on surface bonding of heparin molecules. The natural endothelium actually contains heparin-like molecules, called glycosaminoglycans (GAGs), which contribute to the anticoagulant properties of the endothelium.

Heparin-bonded CPB circuits are associated with a lower activation of the hemostatic system and prevention of platelet adhesion and activation as well as a preservation of platelet count [2–6].

7.2.2 Tissue Factor and Thrombin Generation

Thrombin generation through the material-dependent blood activation alone is by far less pronounced than thrombin generation during CPB [7–9]. Actually, the most powerful trigger for thrombin generation is tissue factor (TF). Soluble TF is released by the damaged endothelial surface, and this release is of course greatly enhanced during surgery. Additionally, cell-bound TF is released by the epicardium, myocardium, adventitia, and bone. In cardiac surgery with CPB, shed blood from the mediastinum is rich of TF, and readmission of this blood into the circulation is the major determinant of thrombin generation [10–12]. In the most recent dynamic interpretation of the hemostatic system activation, small amounts of thrombin are formed

following TF release (*initiation*). Subsequently, thrombin activates platelets through the PAR receptors (*amplification*), and large amounts of thrombin are formed on the platelet surface (*propagation*), finally leading to the conversion of fibrinogen into fibrins (monomers) which are stabilized to fibrin polymers by factor XIII [13].

Once thrombin is formed, it acts as one of the most powerful platelet activators, resulting in platelet consumption and loss of function.

Unlike cardiac surgery, during ECMO, this chain of reactions is limited by the absence of a continuous source of soluble and cell-bound TF. Therefore, the amount of thrombin generated is limited, albeit existent. However, other considerations related to thrombin generation specifically apply to ECMO.

Even if an *acute* pattern of thrombin generation is rarely found during ECMO, the relatively long-lasting characteristics of ECMO treatment (usually in the range of days or weeks) induce a condition of *chronic* thrombin generation. Additionally, many possible factors may enhance TF production during an ECMO treatment. Among them, both the inflammatory reaction and possible patterns of systemic infections may trigger the release of blood-borne TF from leukocytes.

Thrombin generation during ECMO is the reason underlying the need for anticoagulation and is the main trigger for both hemorrhagic and thromboembolic complications.

7.2.3 After Thrombin: The Fibrinolytic System

Once thrombin is formed in excess, a pro-thrombotic state is present. The physiological reaction to this is the activation of fibrinolytic system. Plasminogen is converted to plasmin, through the release of tissue plasminogen activator from the endothelial cells and urokinases from circulating macrophages and fibroblasts or streptokinases from bacteria. Plasmin in turn cleaves fibrin, releasing fibrin degradation products (FDP).

During ECMO, and consequently to chronic thrombin generation, hyperfibrinolysis may occur [14] and could be one of the factors leading to hemorrhage.

7.3 Hemorrhagic and Thrombotic Complications of ECMO

Despite the improvements in techniques and materials, hemorrhagic and thromboembolic complications remain the major threat of ECMO treatment [15, 16], being the most frequent causes of death [17]. Apart from major thromboembolic events, including stroke, mesenteric infarction, and peripheral arterial thrombosis, micro-clot formation has been identified in ECMO patients and is a determinant of ischemic organ dysfunction [18, 19].

There are many factors which contribute to the risk for bleeding and thromboembolic events; they are listed in Table 7.1.

Additionally to these factors, a major role is played by the nature of the ECMO support.

Table 7.1 Main factors contributing to hemorrhagic and thrombotic complications in ECMO

Pro-hemorrhagic factors	Pro-thrombotic factors
Excessive heparin anticoagulation	Inadequate heparin anticoagulation
Consumption of coagulation factors	Acquired antithrombin deficiency
Low fibrinogen levels	Protein C-S complex consumption
Thrombocytopenia	Tissue factor pathway inhibitor consumption
Platelet dysfunction	Endothelial dysfunction
Hyperfibrinolysis	Heparin-induced thrombocytopenia
Acquired von Willebrand disease	Blood stagnation in the cardiac chambers
Surgical site bleeding	Endotoxins

Basically, there is a great difference between venovenous ECMO, peripheral venoarterial ECMO, and postcardiotomy ECMO. Respiratory venovenous ECMO is usually applied through a peripheral cannulation of the femoral veins or jugular + femoral vein or single jugular vein cannulation with a double-stage cannula. Peripheral venoarterial ECMO is usually applied with groin vessels cannulation. Postcardiotomy ECMO is applied in cardiac surgery patients with difficult or impossible weaning from CPB. In this case, different kinds of cannulation may be used. Basically, a peripheral venoarterial ECMO can be placed, or, alternatively, a central cannulation of the right atrium and ascending aorta may be chosen. In this case, specific cannulas can be used, allowing closure of the chest.

However, even when the chest is closed, but particularly in case of open chest, postcardiotomy ECMO carries the greatest risk for severe bleeding. This is due to the fact that the coagulation system is already stressed by the long CPB run and by the great amount of TF and thrombin generated during the surgical procedure; finally, post-surgery hyperfibrinolysis, residual effects of large heparin doses, thrombocytopenia, and surgery itself are other determinants of bleeding. On the other side, intraoperative consumption of natural anticoagulants, like antithrombin (AT), tissue factor pathway inhibitor, and protein C-S complexes, determines a pro-thrombotic condition. As addressed in the following notes on anticoagulation, post-cardiotomy ECMO requires a different approach to anticoagulation and heparin administration, at least during the first hours after implantation.

7.4 Hemostatic System Management During ECMO

7.4.1 Anticoagulation

Systemic anticoagulation during ECMO is intended to control thrombin generation and limit the risk for thrombotic and hemorrhagic complications. Unfractionated heparin (UFH) is the most commonly used anticoagulant [20]. UFH acts by binding and inactivating factor Xa and thrombin; however, heparin is not a direct thrombin inhibitor, and its efficacy is related to the presence of AT. UFH increases the kinetic of the natural thrombin-antithrombin binding by 2,000–4,000 times. Therefore, the efficacy of heparin as an anticoagulant is strongly dependent on the AT

concentration: AT is a sort of “suicide” substrate, and once it is bound to thrombin and factor Xa, it needs to be reconstituted by the liver. As a consequence, chronic heparin administration consumes the endothelial and circulating pool of AT. Additionally, heparin may be bound and inactivated by plasma proteins, endothelial surface, and most of all by circulating platelets, which scavenge heparin by releasing PF4.

Due to this complex scenario, the exact dose required to correctly blunt thrombin generation is undefined and may greatly vary during the course of an ECMO. The classical dose range is reported between 20 and 70 IU/kg/h [20]. However, this dose may vary among individuals and within the same subject, depending on other conditions. Basically, chronic UFH infusion leads to AT consumption and consequently to a lower heparin sensitivity; once AT is corrected, the required dose of UFH decreases. Simultaneously, platelet consumption is inevitable during ECMO, and decreased levels of platelets lead to an increased sensitivity to UFH; again, once allogeneic platelet concentrates are administered and the platelet count recovers, the sensitivity to UFH decreases. Overall, this leads to the need for continuous adjustments of the UFH dose, even if in general there is a trend for larger doses the longer the ECMO system is in place [21].

Even given these limitations, heparin is still necessary while on ECMO, although some authors advocate the possibility of a heparin-free, no-anticoagulation-based ECMO [22–24]. This strategy may be considered in case of excessive bleeding risk, like for trauma patients.

To achieve peripheral vessels cannulation, a small (50–100 IU/kg) bolus dose of heparin is usually administered. In postcardiotomy ECMO, full heparinization is usually already achieved. In this case, a different strategy is suggested: after cannulation and onset of ECMO, heparin should be fully antagonized with protamine sulfate. Subsequently, given the residual effects of CPB and surgery, no heparinization is usually undertaken for the first 12–24 h, to avoid massive postoperative bleeding. Once bleeding is under control, heparin infusion should be started at a low dose (20 IU/kg/h) and subsequently adjusted to the desired level of anticoagulation.

7.4.2 Alternatives to Heparin

Theoretically, direct thrombin inhibitors could be used as an alternative to heparin. This is mandatory in case of heparin-induced thrombocytopenia (HIT).

Bivalirudin is a direct thrombin inhibitor with a short half-life of about 25 min and partial (20 %) kidney clearance [25, 26]. Its use during ECMO has been successfully reported in case of HIT [27–29]; recently, a relatively large series of patients without HIT and treated with bivalirudin as the sole anticoagulant for ECMO has been reported and compared with conventional UFH management [21], with a lower procedural bleeding and less need for allogeneic blood products transfusions.

The dose of bivalirudin is usually reported around 0.03–0.2 mg/kg/h, with [27–29] or without [21] an initial bolus of 0.5 mg/kg.

There are some caveats for the use of bivalirudin in ECMO. The first is that renal clearance may be strongly impaired in case of poor renal function, leading to drug accumulation; the second is that, given its nature, bivalirudin anticoagulation requires no blood stagnation in the circuit or inside the circulation. The ECMO circuit is closed and usually does not present stagnation areas; in venovenous ECMO, there is usually no blood stagnation inside the circulation. Conversely, in case of venoarterial ECMO for cardiac failure, some patients present large areas of blood stagnation inside the left heart chambers, easily detectable as a “smoke effect” at echocardiographic examination. In this case, the risk for cardiac thrombi formation is high, and bivalirudin should not be used [30].

Other direct thrombin inhibitors proposed for ECMO in case of HIT include argatroban [31] (0.1–0.4 µg/kg/min) while danaparoid and lepirudin have been used in the past but are presently abandoned.

7.4.3 Additional Drugs

Antiplatelet drugs have been proposed as additional agents during ECMO, in the attempt to preserve platelet function and prevent aggregation. Some authors propose the use of aspirin (1.5 mg/kg/day) for pumpless arteriovenous ECMO [32]. The use of dipyridamole, once quite popular [33], is presently rarely reported. Apart from anecdotal reports, no evidence exists with respect to the use of antiplatelet agents during ECMO.

Synthetic antifibrinolytics can be used when hyperfibrinolysis is suspected (excessive increase in FDP and D-dimers levels) [34].

The role of AT for the maintenance of a correct thrombin inhibition during UFH therapy has already been highlighted. Inevitably, AT is consumed during ECMO, and the majority of the authors suggest purified AT supplementation aimed to maintain AT activity at the lower normal range of 70 % [35, 36]. Of notice, when bivalirudin is used, AT consumption is strongly limited, albeit present [21].

7.5 Monitoring the Hemostatic System During ECMO

7.5.1 Activated Clotting Time (ACT)

ACT remains the standard of monitoring during heparin anticoagulation in ECMO. The ACT provides a bedside assessment of the intrinsic and common pathway integrity.

During ECMO, the ACT is usually maintained between 180 and 220 s [20]. However, it is well established that the correlation between heparin concentration and ACT is poor during CPB [37, 38]. However, direct measurement of heparin concentration is unpractical, and the optimal level of heparin concentration while on ECMO has not yet been established. Studies confronting heparin concentration with ACT values during ECMO reported variable heparin concentrations between 0.1 and 0.4 IU/mL, with correspondent ACT values ranging from 110 to 220 s [39–41].

7.5.2 Conventional Laboratory Tests

Activated partial thromboplastin time (APTT) explores the intrinsic and common pathways of coagulation and is the classical measure for heparin therapy [20]. APTT poorly correlates with ACT [42]; conversely, it has an acceptable degree of correlation with heparin concentration [43] and is therefore to be considered superior to the ACT for heparin treatment monitoring during ECMO. An APTT of 1.5 times the baseline APTT (50–80 s) is considered the target value during ECMO and corresponds to a heparin concentration of 0.2–0.3 IU/mL [20].

Prothrombin time (PT) is a marker of the extrinsic and common coagulation pathways and should be performed in order to detect the level of coagulation factors and to guide their supplementation with fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), or cryoprecipitates.

Platelet count, fibrinogen levels, and D-dimers assays should be performed daily, since they determine the need for platelet concentrates, FFP, fibrinogen, and antifibrinolytics.

7.5.3 Thromboelastography and Thromboelastometry

Thromboelastography (TEG) and thromboelastometry (TEM) are dynamic tests based on the viscoelastic properties of blood during the coagulation process. In both tests, the time to change the physical nature of blood from liquid to gel (*gel point*) is represented by a straight line and defined as *r time* (TEG) or *coagulation time* (TEM). Once the *gel point* is reached, other parameters represent the kinetic of clot formation (*alpha angle*) and the retraction force of the clot (*maximum amplitude* in TEG and *maximum clot firmness* in TEM). Finally, the decrease over time of the clot strength is an index of fibrinolysis (*clot lysis index* in TEG and *maximum lysis* in TEM) (Fig. 7.1).

TEG and TEM have a number of advantages over the routine coagulation tests. They provide a comprehensive and dynamic analysis of coagulation kinetic, can be done at point-of-care, provide data within about 30 min, and, finally, can be used for detecting hyperfibrinolysis. Therefore, their use for monitoring coagulation and anticoagulation gained wide popularity in recent years.

The *r time* and *coagulation time* are surrogates for thrombin generation and may guide the UFH infusion rate during ECMO. There is not a universally accepted value of *r time* for optimal UFH dose, but the majority of the authors report an optimal window between two and three times the upper normal limit (16–25 min) [20, 21] (Fig. 7.2).

Both TEG and TEM offer an additional number of tests. Adding heparinase, it is possible to detect the “natural” underlying behavior of clot formation. This is particularly useful when the *r time* is excessively prolonged, to distinguish a heparin overload from a coagulation factor deficiency and for guiding the therapy with PCC, FFP, or cryoprecipitates. Specific tests (*functional fibrinogen* in TEG and *Fibitem* in TEM) provide a measurement of fibrinogen concentration (Fig. 7.3). These last values may guide the therapy with FFP and fibrinogen.

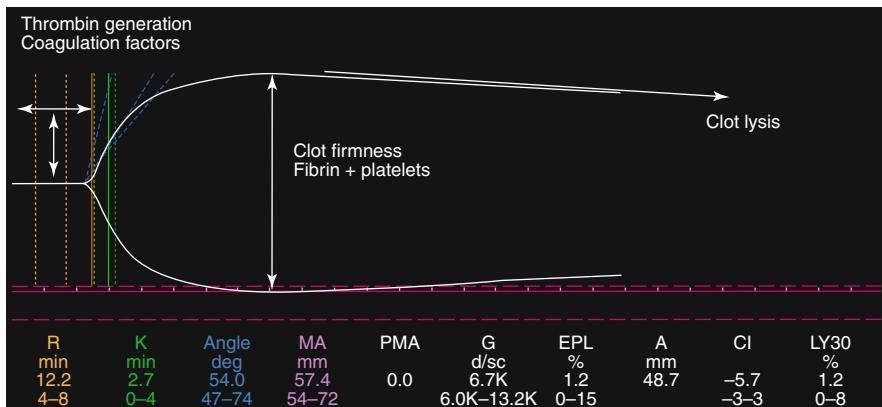


Fig. 7.1 Thromboelastographic tracing

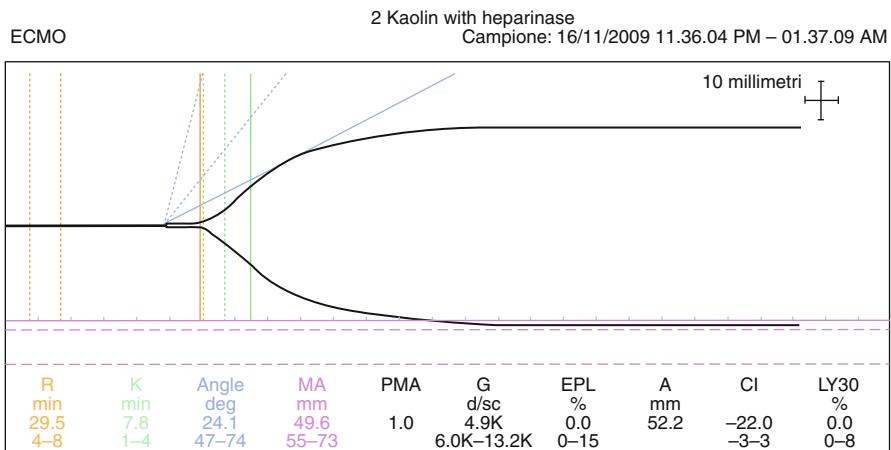


Fig. 7.2 An adequate TEG during ECMO

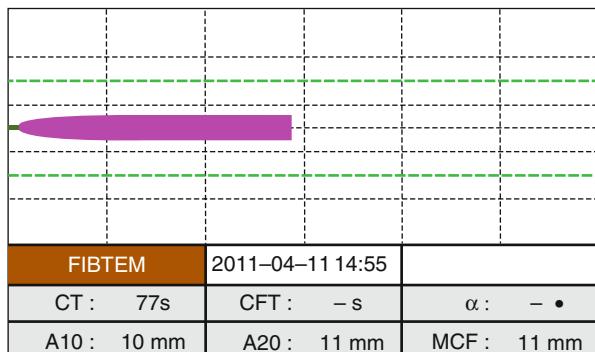


Fig. 7.3 ROTEM analysis for fibrinogen concentration (FIBTEM)

7.5.4 Other Hemostasis and Coagulation Tests

Given the limitations of ACT, and the fact that APTT values may change depending on the laboratory method used, some authors [44] suggested the use of more specific tests for the definition of the UFH infusion rate. The anti-Xa UFH assay measures the anti-Xa activity of heparin in plasma. An optimal value, corresponding to an APTT 1.5–2 times the baseline, is between 0.3 and 0.7 IU/mL [43].

Platelet function analysis with point-of-care tests during ECMO is suggested by some authors [35]. At present, there is a gap in knowledge about platelet function and antiplatelet drugs use during ECMO. There is not a clearly defined cutoff value suggesting platelet concentrate transfusion, and many of the available tests may be biased by the usually low platelet count during ECMO.

7.6 Adjusting the Coagulation Profile

Given the above reported data, it is possible to define an “optimal” coagulation pattern during ECMO. The main key point of this pattern is shown in Table 7.2.

Guiding the patient into the framework of this optimal pattern is one of the most tricky steps during an ECMO management. UFH or bivalirudin dose should be adjusted based on ACT, APTT, and TEG/TEM. The other issues can be adjusted using allogeneic blood products or substitutes.

Purified AT is available for AT supplementation. AT may be administered using FFP, but very large doses are required.

A severe gap in plasma coagulation factors (INR >3) can be corrected with PCC or cryoprecipitates, whereas minor gaps (INR 2–3) could even be treated with FFP.

In case of life-threatening bleeding due to a lack in coagulation factors, recombinant activated factor VIIa (rFVIIa) may be considered. However, this approach has several disadvantages: to be effective, rFVIIa must find an adequate amount of platelets and fibrinogen; additionally, rFVIIa carries the risk for thromboembolic events [45].

Fibrinogen, being an active-phase protein, usually progressively increases during ECMO [21]; however, especially in postcardiotomy ECMO, during the first hours

Table 7.2 The optimal hemostatic pattern for the ECMO patient

Parameter	Suggested value
Activated clotting time (seconds)	180–220
International normalized ratio	1.3–1.5
R time at thromboelastography (seconds)	16–25
Fibrinogen (mg/dL)	>100
Maximum clot firmness at FibTEM (mm)	>10
Antithrombin activity (%)	70–80
Platelet count (cells/mmc)	>80,000 (bleeding patients/high risk) >45,000 (no bleeding/low risk)
d-dimers (μ g/L)	<300

after ECMO implantation, the fibrinogen levels can be very low. Suggested values of fibrinogen should be at least 100 g/dL [20], which approximately correspond to a maximum clot firmness >10 mm at TEM [46]. Fibrinogen concentrate is available for supplementation; alternatively, fibrinogen can be administered as cryoprecipitates or FFP, but again very large doses of FFP are needed.

Antifibrinolytic therapy with epsilon-aminocaproic acid or tranexamic acid should be initiated in presence of signs of ongoing hyperfibrinolysis at TEG/TEM or conventional tests. A certain degree of fibrinolysis is always present during ECMO; values of D-dimers around 300 µg/L are acceptable, but signs of progressive increase suggest a prompt intervention.

Platelet count should be maintained above 80,000 cells/mmc in a patient with active bleeding or at high risk for bleeding, with platelet concentrate transfusions. Conversely, lower values (however >45,000 cells/mmc) may be accepted in non-bleeding patients or patients at low risk for bleeding [20].

All the above figures should however be included within a management based on the actual patient's conditions: a bleeding patient requires a prompt and aggressive approach, with allogeneic blood products and substitutes therapy guided by the whole set of coagulation tests. Conversely, a non-bleeding patient should be treated more conservatively, trying not to treat numbers instead of the patient.

Finally, red blood cells should be administered to maintain a hemoglobin level at a minimal value of 8 g/dL; however, depending on the patient's clinical situation, higher target values may be necessary.

7.7 Particular Conditions During ECMO

7.7.1 Heparin-Induced Thrombocytopenia

HIT is much more common in ECMO and ventricular assist device patients than in the rest of the patient population, with reported rates around 15 % [47, 48]. HIT may be particularly difficult to diagnose, given the presence of many other reasons for a low platelet count. When suspected, HIT should be ruled out with adequate diagnostic tests for the presence of anti-PF4-heparin complex antibodies. If confirmed, heparin should be stopped and replaced with a direct thrombin inhibitor (bivalirudin or argatroban).

7.7.2 Acquired Von Willebrand Disease

Acquired von Willebrand disease is characterized by the loss of the large multimers of the von Willebrand factor, with a consequent defect of the platelet adhesion to the disrupted endothelium. High shear forces produced by centrifugal pumps are responsible for this condition, which is quite common in ECMO patients [49]. However, it is still unclear whether or not this condition is associated with clinically relevant bleeding [49], and the need for a therapeutic approach (factor replacement or desmopressin) remains unclear.

7.8 Systemic Inflammatory Reaction and ECMO

ECMO induces the activation of many inflammatory pathways. Some are directly activated by the contact-phase reaction to foreign surfaces, while others are triggered by TF release and thrombin generation. From this point of view, ECMO is a perfect model for understanding the complex interaction between inflammation and coagulation [50].

Contact with foreign surfaces activates the complement system through the alternative pathway, with the release of the anaphylatoxins C3a (alternative pathway) and C5a (terminal pathway) [51]. Activated complement factors induce the synthesis of cytokines, belonging to both the subgroups of proinflammatory (interleukin-6 and interleukin-8, tumor necrosis factor- α) and anti-inflammatory (interleukin-10) cytokines [52–54]. Proinflammatory cytokines are involved in increased vascular permeability and endothelial dysfunction. Another inflammatory mechanism involves endotoxins. Bacterial lipopolysaccharide is released by gram-negative bacteria and induces TNF- α release by the macrophages [55] and interleukin-6 release by endothelial cells [56]. During ECMO, like in CPB, endotoxins may be released mainly due to bacterial translocation from a poorly perfused gut mucosa [57, 58].

Endotoxins activate circulating monocytes, which in turn release cytokines and blood-borne TF, subsequently activating the coagulation cascade. In turn, the activation of thrombin generation promotes inflammation, leading to a vicious circle.

As for the hemostatic activation, and even to a greater degree, biocompatible surfaces are associated with a blunting of the complement activation, neutrophil activation, and cytokines release [2–6].

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Part II

ECMO for Circulatory Support

Extracorporeal Life Support: Interactions with Normal Circulation

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The end point of any mechanical circulatory support (MCS) is to restore adequacy of perfusion in order to prevent organ damage or to restore normal organ function when damage is already commenced. Reduction of left ventricular end-diastolic pressure, cardiac wall tension, and pulmonary congestion, together with a modulation of the neurohormonal response to acute and chronic heart failure, like endogenous catecholamine, renin-angiotensin system, ANP, and cytokine release, are all aims of mechanical circulatory support.

Myocardial recovery from reversible acute cardiogenic shock or cardiac “reverse remodeling” in chronic heart failure is what we ultimately would like to achieve in our patients. When this is not possible, but recovery of organ dysfunction has been reached, MCS offers other options: bridge to transplant, bridge to bridge, or destination therapy. These end points, in particular destination therapy, can be obtained with left ventricular assist devices (L-VAD). While L-VAD is a one-ventricle support system and requires a normally functioning right ventricle, extracorporeal life support (ECLS) is a bi-ventricular and respiratory support, acting as a heart and lung bypass, thus reproducing the complete cardiopulmonary bypass (CPB) adopted for open-heart surgery.

ECLS, or more commonly ECMO (extracorporeal membrane oxygenation), is nowadays widely used to support the patient’s respiratory system or both circulatory and respiratory systems in life-threatening clinical conditions. The ECLS concept is

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quite straightforward: venous blood is drained from the body into the artificial lung and pumped back into the patient's circulatory system.

The relative simplicity of this circuit though can modify patients' physiology in different ways. In fact, once the patient starts to be supported by ECMO, depending on the type and location of cannulas and according to the underlying clinical conditions, different hemodynamic changes are foreseeable. When blood exiting the artificial lung returns into the patient's venous system, we talk about venovenous ECMO (VV ECMO), and our system is indeed in series with the patient's cardio-pulmonary physiology. When the blood leaving our circuit is returned into the patient's artery, we are talking about venoarterial ECMO (VA ECMO), which is instead parallel. These basic concepts together with the abnormal physiology of the patient needing extracorporeal support must be taken into account when considering the physiology of extracorporeal circulation.

We will look at VA and VV ECMO separately, to analyze how these can impact on circulatory and respiratory systems, and the possible complications that can arise.

8.1 VA ECMO

When venous blood is completely drained by the ECMO pump, whether it is an older roller pump or a more modern centrifugal pump, 100 % of the pulmonary circulation will be bypassed and arterial pulsatility due to residual cardiac activity will cease. Blood flow generated by ECMO will be therefore continuous according to the flattened pulmonary and systemic traces on the monitor. However a certain amount of blood, from the sinus venosus and from the bronchial and Thebesian circulation, will still flow into the left ventricle, which, when adequately preloaded, may have a pulsatile beat. This will appear as an irregular pulsatility on the systemic arterial trace.

Therefore, a complete bypass is possible only when a pulmonary vent is in place, as it happens with the "heart and lung machine" used in cardiac surgery. This cannot be easily obtained by VA ECMO, especially when ECMO is achieved by peripheral cannulation and the heart maintains some residual contractility. As a consequence VA ECMO is considered able to provide about 80 % of the cardiac output at rest, while the remaining 20 % will flow through the pulmonary circulation into the left ventricle. As described below, the incomplete drainage of the cardiac output by VA ECMO could lead to a problematic management of severely compromised patients.

More than one study agree that the level of arterial blood flow, either continuous or pulsatile, must be above 80–90 ml/kg when addressed to counteract cardiac shock, metabolic acidosis, high level of endogenous catecholamines, and the development of low urine output [1]. The critical threshold is considered to be 40–50 ml/kg. Below this, inadequate oxygen delivery, cardiocirculatory shock, anaerobic metabolism, and acidosis will occur independently of the type of blood flow. At intermediate levels, pulsatile flow can partially compensate the effect of hypoperfusion and acidosis. This is because aortic and carotid baroreceptors are strongly stimulated by non-pulsatile flow with consequent release of endogenous catecholamines and deleterious effects on the microcirculation [1].

Usually VA ECMO is started at 2.6 l/m^2 , and adequate systemic blood flow and oxygen supply are guaranteed by parameters listed in below

Pump flow $>2 \text{ l/min/m}^2$

Ht $>33\%$

$\text{PaO}_2 >100 \text{ mmHg}$

MAP = 60–90 mmHg (vasodilators or vasopressors)

Oxygen delivery will be mostly determined by hemoglobin level and extracorporeal blood flow, while the ECMO oxygenator can easily modify PaO_2 .

Physiologic values of mean arterial pressure are necessary to provide adequate tissue perfusion and can be modulated with the appropriate use of vasodilators or vasopressors. When considering mean arterial pressure, though, the level of systemic vascular resistances must be taken into account as the efficacy of the centrifugal pump (differently from the roller pump), and therefore the resulting blood flow depends not only on the amount of venous blood drained (preload) and the pump power (RPM) but also on the resistances created by the circuit and the patient's vascular system (afterload).

Clinically, normal skin temperature, normal capillary refill time, arterial blood pH normalization, reduction of lactates, and increased urine output are all signs of improved patient perfusion. It is worth noting that non-pulsatile flow can have an antidiuretic effect by direct stimulation of the juxtaglomerular apparatus. This is usually easily controlled by low doses of diuretics [1].

The use of the mixed venous saturation value (SvO_2) from pulmonary artery catheter as a parameter of good peripheral perfusion deserves special mention when considered in a patient on VA ECMO. As a matter of fact we can sometimes see abnormally high values of SvO_2 , which do not reflect the real relation between DO_2 and VO_2 but, instead, a phenomenon of equilibrium with pulmonary capillary blood (retrograde flow hypothesis).

This can be seen when ECMO is achieving almost complete bypass of the pulmonary circulation, and therefore, pulmonary artery blood flow is low. Paradoxically, as the patient recovers, the SvO_2 will decrease: this occurs because as the percentage of cardiac output passing through the native heart and pulmonary circuit increases, the PaO_2 will decrease [2]. The ETCO_2 values can help us better understand our data. An increase in ETCO_2 values as well as a reduction in alveolar-arterial CO_2 difference are indirect indices of increased pulmonary blood flow. This can be taken into account when dealing with weaning from ECMO. Alternatively, a more accurate assessment of venous saturation can be obtained by analyzing blood before entering the oxygenator or directly at the right atrium (ScVO_2).

An additional “fringe benefit” rarely underlined is that, during ECMO, the patient's temperature is easily controlled, thus avoiding detrimental increases in VO_2 , and when needed, moderate protective hypothermia can be instituted [3, 4].

During VA ECMO, the suction of blood from the central venous system determines right ventricle unloading. However, adequate left ventricle unloading can be problematic, and this will be considered when adjusting the level of ECMO

support or the patient therapy. The reasons behind inadequate left ventricle unloading of the patient on ECMO are different and not always obvious and are to be found both on preload and afterload of the left ventricle. As stated previously, while ECMO owes its origins to the heart and lung machine, its setup is indeed different. The lack of a venous reservoir and left ventricle venting, in order to simplify the system to a bedside support and to allow, when needed, percutaneous access, has, as side effect, a certain amount of blood not drained. As such, the bronchial and Thebesian blood flow will continue to fill the left-side cavities. If residual myocardial contractility is not enough to provide stroke volume, this gradual and continuous filling will eventually lead to overdistension and high pressure in the left atrium and left ventricle. Therefore, even though the unloading of the right ventricle determines a reduction in pulmonary blood flow, left ventricle preload can still be problematic.

Bavaria and colleagues [5] demonstrated that VA ECMO decreases left ventricle wall stress in normal hearts. However, a progressive rise in wall stress in postischemic hearts occurs with an increase in ECMO flow rate as a result of a concomitant increase in afterload. Left ventricle afterload increases as a consequence of blood return via the arterial cannula, and this is of particular concern in peripheral VA ECMO [6].

The combination of increased afterload from the arterial cannula and the underlying myocardial dysfunction can lead to high values of left atrial and left ventricular end-diastolic pressure. This will increase wall stress and myocardial oxygen consumption, worsening left heart failure. Increased left atrial pressure, even more relevant if associated with severe mitral regurgitation, results in pulmonary congestion, pulmonary edema, and in extreme cases, pulmonary hemorrhage which can lead to irreversible pulmonary failure. When severe left ventricular dilatation and dysfunction are present, the left ventricle may become unable to generate enough pressure to actually open the aortic valve. This will appear as a loss of pulsatility on arterial pressure tracings and can lead to stasis and thrombosis in the ascending aorta, left ventricle cavity, and pulmonary veins. In this case, anticoagulation must be carefully titrated, and left ventricle afterload must be reduced by optimizing native left ventricle output, thus facilitating aortic valve opening.

As previously stated, blood flow generated by the ECMO pump is countercurrent to that coming from the heart. It follows that the upper and lower parts of the body could receive differently oxygenated blood. Areas closer to the outflow cannula (i.e., arterial cannula) will receive blood straight from the oxygenator, rich in oxygen and cleared of carbon dioxide, while those areas further away from the ECMO oxygenator, but closer to the left ventricle outflow, will receive blood that is oxygenated and cleared of carbon dioxide from the native lungs. There is then a third area where O₂ and CO₂ content will be a flow-weighted average of the O₂ and CO₂ contents of two flows.

The exact location and prevalence of these three areas vary according to the type of support (central vs peripheral) and the level of flow (high vs low ECMO flow).

In case of peripheral ECMO, where arterial flow is delivered through the femoral artery, a low flow will determine a good oxygenation of subdiaphragmatic regions, a mixed zone at thoracic descending aorta, while blood flowing through supra-aortic

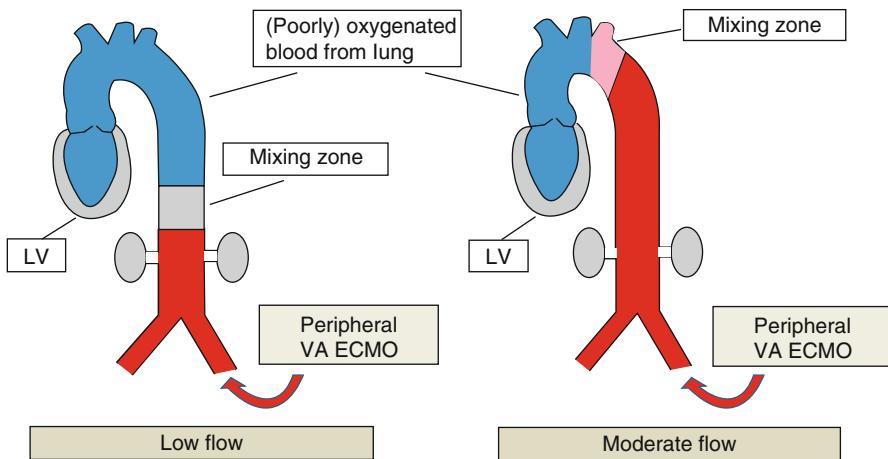


Fig. 8.1 Distribution of arterialized blood during peripheral VA ECMO with low (*on the left*) or moderate flows (*on the right*) delivered to femoral artery. If there is significant pulmonary parenchymal disease or inadequate mechanical ventilation during ECMO support, hypoxic blood returning to the LV provides the sole source of myocardial and cerebral perfusion

vessels and coronary arteries will be that coming from the patient's native lungs (Fig. 8.1, left).

When a moderate level of flow is used in the setting of peripheral ECMO (Fig. 8.1, right), the area of mixed blood is shifted towards the left subclavian artery. In this situation, in case of concomitant impairment of pulmonary function, we could witness the Harlequin syndrome: locoregional and asymmetric discrepancies in blood flow distribution appearing as differences in skin color, in different parts of the body, with the result of a patient with a "blue head," "red legs," and different oxygen saturation between the left and right arm.

Possible strategies, in case of hypoxemia to the supra-aortic territories, are:

- Increase oxygenator FiO_2
- Increase pump speed and pump flow in order to obtain maximal RV and LV unloading, decrease blood flow through inefficient lungs, and shift competitive blood flow before supra-aortic arteries

In the latter option, when pump speed and flow are increased, coronary flow would be provided by the left ventricle (i.e., with blood coming from the patient's native lungs) and only if there is any appreciable ventricular ejection, while oxygenated blood from the arterial cannula may fail to reach the coronary artery [7, 8] (Fig. 8.2, right).

Optimal coronary oxygenation can be obtained through central VA ECMO (Fig. 8.2, left), whether this is intrathoracic (outflow cannula directly in the ascending aorta) or extra thoracic (outflow cannula in the right subclavian artery or the right carotid artery) at the expense of a possible higher afterload when compared with peripheral VA ECMO. Direct venting of the LV can obviate to this problem and is easy to obtain in central intrathoracic ECMO.

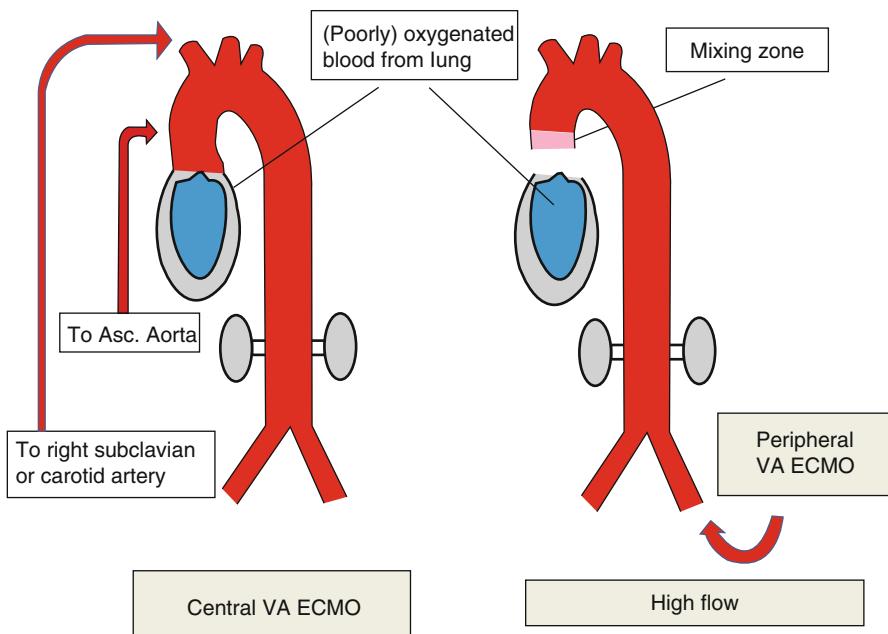


Fig. 8.2 Distribution of arterialized blood during peripheral VA ECMO with high flow delivered to femoral artery (*on the right*) and during central VA ECMO with flow delivered to aortic root (*on the left*)

Peripheral VA ECMO can therefore worsen myocardial damage through inadequate oxygenation of the blood reaching the coronary arteries [8, 9]. When pulmonary gas exchange is severely impaired by parenchymal disease and pulmonary edema, or when the setting of mechanical ventilation is not adequate, hypoxic blood returning to the left ventricle may provide the sole source of coronary perfusion with deleterious effects on ventricular function and myocardial recovery [10]. Concomitant clinical conditions like sepsis, acidosis, or hypoxia may contribute to the decrease in cardiac performance.

Inadequate perfusion of the coronary arterial flow may also occur: the increase in left ventricular end-diastolic pressure during VA ECMO could result in an increase in coronary vascular resistance and consequent decrease in coronary flow.

Physiologically, the aortic root expands during systole, and it acts as a blood reservoir for coronary perfusion in diastole. The lack of pulsation during ECMO, as well as a decrease in cardiac output, will result in a reduction of this function. In addition, cardiac output is decreased in inverse proportion to the ECMO flow. Therefore, coronary arterial flow could decrease as VA ECMO flow increases so that high-flow VA ECMO could exert undesirable hemodynamic effects on the left ventricle. Therefore, especially when dealing with peripheral VA ECMO, extreme care must be taken to ensure that the heart is ejecting adequately oxygenated blood to perfuse not only the coronaries but also the cerebral circulation, thus avoiding disastrous anoxic/hypoxic injuries. Inadequate saturation may not be immediately obvious: peripheral arterial blood gas analysis, according to the ECMO setting,

could show fully saturated blood and may not reflect the oxygen level in the aortic root. In peripheral ECMO, right radial arterial analysis may better reflect the level of blood oxygenation to the heart and brain and unmask the oxygenation discrepancy between the upper and the lower half of the body. At this level it is possible to see the actual saturation of the blood that perfuses the myocardium as well as the brain and to realize whether there is an oxygenation discrepancy between the upper and the lower half of the body. To correctly monitor saturation in the supra-aortic areas, the placement of a saturation probe at the right earlobe or right hand is advisable. NIRS is another useful parameter addressed to monitor cerebral oxygenation in a continuous fashion especially because it is not influenced by the absence of arterial pulsation.

The combination of left ventricle distension, augmented afterload from arterial peripheral cannula, inadequate oxygenation of the myocardium by inefficient coronary perfusion, associated with the underlying disease, metabolic acidosis and pulmonary dysfunction can together lead to progressive worsening of left ventricle function. Insufficient left ventricle unloading can lead to pulmonary congestion and lung edema and blood stagnation in the left ventricle with an increased risk of systemic embolic complications and, ultimately, hinder myocardial recovery.

Rhythm instability, ventricular fibrillation, and asystole may supervene when a patient is supported on ECMO. When such rhythm alterations are present, even if systemic perfusion is adequately maintained by the extracorporeal system, these will further worsen inadequate left ventricle unloading. For all these reasons it is abundantly clear why adequate unloading of the left ventricle during VA ECMO is of extreme concern.

Different strategies can be used to avoid these possible complications. Restoration of an adequate perfusion rhythm is essential. Then, sufficient inotropic support should be maintained in order to improve left ventricular contractility and to reduce left ventricular distension [11] and clot formation, even when VA bypass can provide adequate systemic pressure.

In situations of severe myocardial dysfunction, when the heart is unable to generate enough force to open the aortic valve and overcome pressure created by the AV circuit, systemic vascular resistances need to be decreased with the appropriate use of vasodilators [12].

The combinations of ECMO and intra-aortic balloon pump (IABP), when feasible, can be extremely beneficial. IABP improves diastolic filling and lowers coronary vascular resistances, thus improving coronary blood flow. Moreover, intra-aortic balloon counterpulsation alone significantly reduces afterload, thus reducing myocardial wall stress and oxygen consumption, and ultimately improves contractility and myocardial recovery. IABP has the additional advantage, like peripheral ECMO, that it can be quickly inserted and started at the bedside, with minimal or no surgical intervention. Because of this beneficial effect, the concomitant use of IABP and ECMO is recommended [13–15]. In those cases in which the use of catecholamines together with vasodilators and IABP is not sufficient to adequately unload the left ventricle, left-side venting should be considered. Direct insertion of a vent in the left atrium or left ventricle can be accomplished through thoracotomy [16]. However, the risk of bleeding is significant in patients on ECMO, especially if we are not in

the setting of central ECMO and the chest has not been previously opened. Other less-invasive methods to vent the left ventricle have been described widely in the literature: transseptal atriotomy creating a small atrial septal defect under fluoroscopic guidance [17], anterograde left ventricle unloading through a transaortic venting catheter [18, 19] or catheterization of the pulmonary artery by a small catheter to allow retrograde decompression into the right atrium [20–22]. Several recent reports have described the successful use of an Impella Recover 2.5 as a vent for the left ventricle [23, 24]. The use of transthoracic and transesophageal echocardiographic guidance has also been described to perform atrial septostomy [25].

In order to preserve long-term patient homeostasis and avoid or treat organ damage, maintenance of adequate level of venous pressure is important as well. Among splanchnic organs, the liver appears to be the most vulnerable to hypoperfusion. Cardiac failure-induced hepatic dysfunction may progress despite adequate hemodynamics with mechanical circulatory support. Systemic hypotension alone does not account for hypoxic hepatitis, while venous congestion predisposes the liver to injury induced by a hypotensive event [26]. Any higher pressures in the venous system of the body will interfere with portal circulation because of the low-pressure gradient and the absence of a valvular mechanism available in this circulation. A reduction in portal vein flow is also caused by concomitant vasoconstriction due to systemic neuroendocrine responses.

Diminished O₂ supply to the liver due to reduced portal venous flow together with hepatic congestion could cause hypoxia of hepatocytes (“hepatic hypoxia”), which causes centrilobular damage. The biological hallmark of centrilobular liver cell necrosis is a massive increase in serum aminotransferase levels. It is therefore necessary to keep the venous pressure as low as possible to preserve the portal circulation. Maintaining a low CVP will affect not only the liver function but also the renal and intestinal circulation [27].

8.2 VV ECMO

Venovenous bypass, in general, has no major hemodynamic impact, because blood is drained from, and returned to, the right ventricle without a specific change in right ventricle preload and with no adverse effect in case of a normally ejecting left ventricle. Despite this, hemodynamic derangement is often observed when the bypass starts: several reasons have been proposed (dilutional hypocalcemia or catecholamines, respiratory alkalosis, hypothermia); in order to minimize this alteration, a very slow increment of extracorporeal blood flow is recommended.

Some aspects though need to be considered, especially when the right ventricle is failing to eject against high pulmonary pressures. RV function may be adversely impacted by significant hypoxemia, subsequent increase in pulmonary vascular resistance, and possible concomitant sepsis. When a patient is supported by VV ECMO, the level of mechanical ventilation is usually lowered towards protective

lung ventilation or, at times, even suspended. The consequent reduction in intrathoracic pressures will determine a reduction in pulmonary resistances and an increase in right ventricular preload and contractility. Venous oxygen saturation is increased during VV ECMO, and therefore the pulmonary circulation is perfused with blood high in oxygen content. The reduction in pulmonary vascular resistances that this causes will positively lower right ventricle afterload. Moreover, improvement in left ventricle contractility may also be observed secondary to an increase in oxygenation of the myocardium through coronary arteries. The overall increase of heart oxygenation, in the absence of any hemodynamic interference, explains the possible beneficial effect of VV ECMO on the patient's hemodynamics. Correction of acidosis and clearance of carbon dioxide will also lower pulmonary pressures and improve cardiac contractility [28, 29].

Ultimately, reducing pulmonary vascular flow potentially modulates the endothelial activation and aggravation of pulmonary edema secondary to reperfusion injury.

A special consideration should be paid to the common parameters used to monitor critically ill patients: SvO_2 is abnormally elevated depending mainly on the ratio of extracorporeal blood flow/cardiac output, and it loses its meaning to reflect the adequacy of tissue perfusion. However the arterial to venous gap gives consistent information on the amount of gas exchange through the natural lung.

VV ECMO can alter PaO_2 in completely opposite ways: most of the time the increase of oxygen content provided by the artificial lung, increasing the PvO_2 , is followed by the increase of PaO_2 (i.e., provided that the amount of oxygen transfer through the natural lungs is constant: the higher the PvO_2 , the higher PaO_2 will be); however, if respiratory acidosis, hypercapnia, and venous low oxygen are corrected by VV ECMO, pulmonary vasoconstriction is relieved, and a different V/Q match is obtained [30].

Clinical advantages of VV ECMO include relative technical ease of cannulation, increased aortic oxygen saturation, reduced risk of systemic embolization, and the possibility of a higher flow rate, but on the other hand, this does not provide any circulatory support.

VA approach instead provides circulatory support to facilitate early recovery from the ALI process and provides relief of the pulmonary circulation and reduction of high pulmonary pressure, almost uniformly present.

The most beneficial type of ECMO, whether it is VA or VV, when dealing with primary graft dysfunction after lung transplantation is still a matter of debate and varies from center to center. It is clear that both techniques have their pros and cons.

8.3 Conclusion

The influence of an extracorporeal support on homeostasis is substantial and differs depending on the type of cannulation used. The pathophysiologic derangements should guide the clinician to the type of support required.

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9.1 Introduction

Cardiogenic shock (CS) is defined as a state of tissue hypoperfusion induced by cardiac failure after correction of preload [1].

Although it can be induced by virtually every cause of myocardial dysfunction, acute myocardial infarction (AMI) and its complications represent the leading cause of CS. Other common causes include postcardiotomic shock, myocarditis, pulmonary embolism, and acutely decompensated chronic heart failure.

The incidence of CS in patients with AMI is of 6–7 % in recent datasets [2], although these figures are very likely underestimated since they do not take into account prehospital deaths. Despite improvements in supportive therapies and reperfusion strategies, the mortality rate remains unacceptably high and CS represents the most common cause of death in patients hospitalized for AMI.

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In this dramatic setting, the prompt institution of a peripheral mechanical circulatory support is able to stabilize the patient and buy time for diagnostic and therapeutic procedures, which can be carried out while maintaining an adequate tissue perfusion.

9.2 Epidemiology and Pathophysiology

The true incidence of CS is difficult to determine, as prehospital deaths are not accounted for. Moreover, different definitions across the literature lead to important variations in the reported rate.

The first reported note of cardiogenic shock in the setting of AMI dates back to 1794, while Griffith and colleagues published the first large case series in 1954. In this report, the authors described an incidence of 19.7 % of CS among patients admitted to the hospital for AMI, with a mortality rate of 80 % [3].

From those early days, several changes were introduced in clinical practice: the introduction of coronary care units, the intra-aortic counterpulsation, the first experiences with mechanical circulatory support, the pulmonary artery catheter, and the percutaneous and surgical revascularization techniques, to name the most relevant.

In the face of all these innovations and the observed reduction of CS in patients with AMI, only a modest reduction in mortality was recorded in patients who eventually develop cardiogenic shock. In fact, Goldberg and colleagues reported a mortality rate of 65.4 % in AMI patients who develop CS, as compared to a 10.6 % in those without CS [2].

CS is associated with elevated mortality and morbidity despite the use of conventional therapy with inotropic agents and intra-aortic balloon pump (IABP). In the recently published IABP-SHOCK II, the use of IABP for the treatment of advanced CS did not appear to improve the early outcome in patients with AMI complicated by heart failure [4]. Although the results of this trial were criticized, these must be taken into account.

CS is often a complication of ST elevation myocardial infarction – particularly anterior AMIs – but non-ST elevation infarctions can also result in cardiogenic shock. Autopsy studies suggest that the loss of more than 40 % of LV myocardium is required to develop cardiogenic shock, in the absence of a mechanical complication [5–7]. CS can also be a sequel of a mechanical complication of infarction, such as a ventricular septal defect, left ventricle free wall rupture, or acute mitral regurgitation due to papillary muscle rupture.

Risk factors for the development of CS include older age, prior myocardial infarction, female gender, diabetes mellitus, and anterior MI.

The initial occlusion of the coronary artery initiates a vicious circle leading to a progressive worsening in myocardial function. Myocardial ischemia impairs myocardial contractility and leads to a reduction in ventricular performance with a consequent reduction in arterial pressure and hence in coronary perfusion pressure. Together with an alteration in oxygen extraction and the loss of coronary autoregulation, this leads to further extension of the ischemic insult. Preload is initially increased

by renal compensatory mechanisms leading to fluid retention, whereas the vasoconstrictor response to hypotension increases afterload and oxygen consumption. Increased demand and inadequate perfusion further worsen myocardial ischemia and cardiac function, and if this vicious circle is not promptly interrupted, it can lead to irreversible shock and ultimately to death. The pathophysiological concept of combined low cardiac output and high systemic vascular resistances has been recently challenged by the observation that post AMI, CS may be associated with relative vasodilation rather than vasoconstriction. This is likely due to a systemic inflammatory response syndrome (SIRS) similar to that seen in sepsis [8] due to an inappropriate production and utilization of nitric oxide, which in turn leads to vasodilation with reduced systemic and coronary perfusion pressures. Lim and colleagues found that several patients with CS died despite normalization of their cardiac index, suggesting a maldistribution effect with low systemic vascular resistance [9].

Another important cause of CS in AMI is ischemia remote from the infarct zone. The typical response of the uninjured myocardium during AMI is represented by a compensatory hyperkinesis. Patients who develop CS on the contrary generally present with a multivessel coronary disease so that several perfusion territories demonstrate a pressure-dependent perfusion [10].

A further impairment of the ventricular function is determined by the extension of the ischemic area to adjacent myocytes. These are particularly susceptible to ischemia and have a reduced reserve to face inadequate perfusion and the increase in oxygen demand imposed by endogenous and exogenous catecholamines.

Stunned and hibernated myocardium represent an additional cause of cardiogenic shock in the acute phase, but their function can be restored if these regions are properly managed and promptly revascularized, and contribute to recovery. “Hibernation” follows the restoration of a nearly normal perfusion. Oxidative stress leads to an altered response of myofilaments to calcium, which in turn causes damage in the contractile apparatus when the myocardium is reperfused [11]. The recovery of oxidative lesions and the resynthesis of contractile proteins seem to be the mechanism of hibernated myocardium recovery which is observed up to 6 weeks after the primary insult.

Right ventricular AMI can also lead to CS with a slightly different mechanism. The impairment in both diastolic and systolic dysfunction of the right ventricle results in a volume-sensitive state in contrast to the pressure-sensitive state seen in left ventricular infarction [12]. The ensuing damage may be unresponsive to fluids and lead to a poor prognosis.

9.3 Clinical Presentation and Diagnosis

The recognition of CS is founded on clinical and hemodynamic parameters. Patients present mostly hypotensive, with signs of inadequate peripheral perfusion (altered sensorium, cool extremities, oliguria, acidosis).

There are no sharp cutoff values to define the hemodynamics of CS. However, generally accepted parameters include a systolic blood pressure of less than

Table 9.1 Cardiogenic shock criteria

<i>Hemodynamic criteria</i>
Systolic blood pressure (SBP) below 90 mmHg (or more than 30 mmHg below basal in hypertensive patients) for more than 30 min
Use of vasopressors and inotropes to keep SBP above 90 mmHg
Cardiac index of less than 2.2 L/min/m ²
Pulmonary artery occlusion pressure of above 15 mmHg
<i>Signs of tissue hypoperfusion</i>
Pale, cool, and clammy peripheries
Prolonged capillary refill times
Altered sensorium
Oliguria/anuria (less than 0.5 mL/kg/h)
Signs of pulmonary congestion
Tachycardia
Lactic acidosis
Mixed venous saturation below 65 %

90 mmHg for more than 30 min, a mean arterial blood pressure below 60 mmHg, oliguria (less than 0.5 mL/kg/h), a cardiac index of less than 2.2 L/min/m² with inotropic support or less than 1.8 L/min/m² without support, and elevated filling pressures (left atrial pressure above 18 mmHg and/or right atrial pressure greater than 15 mmHg, pulmonary artery occlusion pressure more than 15 mmHg). Hypotension may in part be compensated by a marked elevation in systemic vascular resistance (SVR), mediated by increased release of endogenous vasoconstrictors such as norepinephrine and angiotensin II. This deadly combination of a low cardiac output and elevated SVR may result in a further reduction in tissue perfusion.

Diagnostic criteria for CS are summarized in Table 9.1.

Other causes of shock (distributive, hypovolemic, and obstructive) must be ruled out and contributing factors – such as hypovolemia, hypoxia, and acidosis – must be corrected in order to determine the etiology of shock.

Echocardiography represents a fundamental tool in the diagnostic workup of CS. Nonischemic causes of CS can be investigated: pericardial effusions, valvular abnormalities, and acute overload signs such as in massive pulmonary embolism and volemic status but also mechanical complications of MI. It also allows quantification of the severity of cardiac involvement and evaluation of systolic and diastolic function and regional abnormalities.

Echocardiography should nowadays be applied as a first-line diagnostic technique together with traditional hemodynamic tools in a so-called echodynamic approach to CS and to any cause of hemodynamic instability.

The presence of current myocardial ischemia must be assessed and appropriate investigations must be performed. In this regard, coronary angiography should be performed in all patients with cardiogenic shock in whom acute myocardial infarction is suspected and who are candidates for revascularization with either percutaneous coronary intervention or coronary artery bypass graft surgery. In addition, all patients who have undergone reperfusion therapy should be evaluated for failure of reperfusion.

9.4 Management

Prompt restoration of adequate blood flow to the affected myocardium is the key management measure in all patients with ongoing ischemia.

Systemic thrombolysis, percutaneous coronary revascularization (PCI), and surgical revascularization represent the available alternatives.

Thrombolysis should be restricted to patients who would have otherwise no chance of timely reperfusion, as in CS its likelihood of success is reduced by both the low coronary blood flow and the hostile biochemical environment [13].

PCI represents the optimal treatment for patients in whom CS developed early after myocardial infarction and the coronary anatomy makes it feasible.

Surgery may allow a more complete revascularization, but it is more invasive and requires longer times to reperfusion. It is better reserved to patients in whom PCI is impossible for any technical or clinical reason [14].

Of course, the need for a prompt myocardial reperfusion should not de-emphasize the concurrent necessity to sustain the patient's hemodynamics, restore an adequate tissue perfusion, and reverse metabolic derangements.

Fluid replacement and supplemental oxygen when needed are the basic measures. If respiratory failure is severe, ventilatory support (either noninvasive or invasive) should be provided.

Optimization of myocardial performance is generally sought with the use of catecholamines. Although they are frequently needed to increase tissue perfusion, this can be seen as a "palliative" therapy, as no evidence of survival benefit exists with the use of such drugs, which might on the contrary worsen myocardial dysfunction by increasing myocardial oxygen consumption [15, 16]. The dosage of inotropic agents should be continuously titrated to the minimum necessary dosage needed to achieve the therapeutic goals, in order to minimize oxygen consumption and arrhythmogenic effects. An interesting alternative with regard to myocardial oxygen consumption is represented by the class of calcium sensitizers, levosimendan being the only compound currently available on the market. Since its positive inotropic effect is based on a reversible increase of the affinity of the myocardial contractile apparatus to calcium and not on the increased influx of calcium, it does not increase myocardial oxygen consumption nor has an arrhythmogenic effect. Moreover, both its peripheral vasodilatory and anti-inflammatory effects might also be useful in the setting of CS [17–19].

In many patients, fluids and inotropes alone are unable to stabilize hemodynamics. In such cases, a mechanical support device is needed.

The simplest form of mechanical support is represented by intra-aortic balloon counterpulsation (IABP). The rationale for aortic counterpulsation is particularly strong in the setting of myocardial ischemia and infarction and in postischemic acute mitral regurgitation, for its positive effects on coronary perfusion and afterload reduction.

The benefit of IABP on early mortality in patients with CS has been recently questioned by the results of the IABP-SHOCK II Trial [4]. These results were quite surprising, but the trial raised many criticisms, and a change in the current guidelines based on this evidence seems unjustified at the moment.

IABP may be unable to adequately support a patient with severe CS, especially when a large portion of the myocardium (more than 40 % on average) is affected. It is generally accepted that a cardiac output of at least 2.5 L/min is needed for the patient to take advantage of counterpulsation.

In such a condition, a full mechanical circulatory support (MCS) must be considered and, if indicated, implanted as early as possible.

MCS is required to rapidly improve the coronary perfusion, unload both ventricles, decrease the oxygen myocardial demand, and maintain end-organ perfusion. Currently, there are several MCS devices available, such as extracorporeal membrane oxygenation (ECMO), paracorporeal or extracorporeal ventricular assist devices (VADs), percutaneous VADs, and total artificial heart (TAH). Most of them are particularly expensive and need time and a surgical approach for implantation. ECMO represents an ideal choice for these patients because of the quick and easy insertion of this device even during fatal arrhythmia or cardiac arrest. With respect to surgically implanted VADs, ECMO offers some unique advantages in that it is readily available to provide circulatory support, with the ability to resolve organ injury in patients who present with cardiac arrest or with severe hemodynamic instability associated with multiorgan failure.

9.5 Role of ECLS

Whenever ECLS is deemed necessary to support a patient in CS, this should be set up without delay, as the early introduction of ECMO has been related with better clinical outcome and hospital survival [20]. MCS can interrupt the inflammatory cascade initiated by the onset of shock and prevent progression to irreversible end-organ damage and subsequent death; however, a window of opportunity remains during which rescue is possible.

Each patient should be considered as a candidate for ECMO; however, not all patients affected by refractory CS meet the criteria for ECMO institution (Table 9.2).

Several considerations must be taken into account in order to determine a patient's eligibility for ECLS. Candidates should be selected only if significant organ recovery is expected or there is no contraindication to long-term mechanical support or transplant.

Table 9.2 Contraindications to ECMO institution

Advanced age (more than 75–80 years old)
Disseminated malignancy
Severe degenerative brain disease
Unwitnessed cardiac arrest
Prolonged CPR time (more than 45–60 min)
Aortic dissection
Severe peripheral vasculopathy
Irreversible renal disease (dialyzed patients)
Severe aortic regurgitation
Ungraftable coronary arteries
Non-eligibility to heart transplant or VAD

Up to 60 % of survivors cannot be weaned and require a ventricular assist device (VAD) or transplantation [21, 22]. ECMO may therefore provide a bridge to decision; it is less costly than VADs, can be initiated quickly, and offers biventricular and respiratory support, thereby stabilizing patients while their suitability for a VAD or transplant is evaluated. Institutions that do not provide this therapy should consider referring patients to an experienced center once IABP support has been initiated. In these situations, expert retrieval teams from the specialist center should provide transport [23, 24].

The ideal indication for ECMO institution is isolated severe heart failure in the absence of signs and symptoms of multiorgan failure.

Factors such as age, comorbidities, and neurological, renal, and hepatic status could preclude ECMO institution. The most common contraindications to ECMO are based on irreversible multiorgan failure, severity of cerebral damage, and absence of chances for recovery in patients who are not candidates for heart transplantation or long-term VAD implantation.

ECLS is able to stabilize the majority of patients, prevent organ dysfunction, and revert metabolic derangements, provided it is implanted in a timely fashion. Its positive effect on mid- to long-term outcome appears reasonable, with reported survival rates of 20–43 % among patients who received ECLS for cardiac arrest, severe cardiogenic shock, or failure to wean from cardiopulmonary bypass following cardiac surgery. The evidence is however quite weak due to the small numbers of observational studies and case series and the lack of RCTs.

Our group, as well as Combes and coworkers, demonstrated a 28–31 % survival to discharge in patients supported with ECMO for postcardiotomic or post-AMI shock refractory to conventional management including IABP [21, 25].

The pooled data from the ELSO (Extracorporeal Life Support Organization) Registry report an average survival rate of 39 % for adult patients with cardiogenic shock [26]. These results are consistent with the recent report from Sakamoto and colleagues. In a population of patients with acute coronary syndromes complicated by cardiogenic shock or cardiac arrest, they demonstrated a 32.7 % survival to hospital discharge. The extrapolation of data on the circulatory status at the onset of ECMO reveals a 41 % survival to discharge in patients with CS, with the circulatory status being one of the independent predictors of in-hospital mortality at multivariate analysis, together with failed angioplasty and ECLS-related complications. Interestingly, univariate analysis showed a significant negative impact of the time from collapse to ECMO on mortality [27]. This was lately confirmed by Kim and colleagues, who also noted an association between pre-ECMO lactate levels and mortality [28].

Moreover, Bermudez and colleagues recently reported what is common gut feeling: patients presenting for an acutely decompensated chronic heart failure do much worst on ECMO than patients with acute cardiogenic shock, with 2-year survival rates of 11 and 48 %, respectively [29].

Similar results have been reported in a number of small studies and case series.

The available evidence and clinical current practice suggest a careful selection of potential candidates to ECLS and the prompt institution of the extracorporeal support in order to prevent progression of distal organ failure and avoid the progression to an irreversible degree of multiple organ dysfunction [30].

9.6 Patient Care During ECLS

As stated before, extracorporeal support should be commenced as soon as it becomes necessary, avoiding unnecessary and deleterious delays.

Cannulation techniques are described elsewhere in this book.

Once implanted, ECMO management should follow a standardized protocol, though individualized on each patient's needs.

General issues on anticoagulation, all aspects pertaining to patient care, strategies to enhance rest and recovery of the heart, and weaning from ECLS are presented in specific chapters across the book.

We will here focus on few specific aspects of post-AMI patients.

9.6.1 Interventions to Promote Heart Rest and Recovery

Myocardial revascularization should be performed immediately in all AMI patients who could not be revascularized before ECMO initiation, as patients in CS are particularly likely to benefit from early revascularization [31].

If an IABP is already in place, it is reasonable to keep it whenever possible; however, no clear evidence exists on its benefit during peripheral ECMO. It is hence not recommended at present to suggest the placement of an IAB in all patients. Nevertheless, the use of counterpulsation has several potential advantages in this setting: it helps in unloading the left ventricle, augments coronary perfusion pressure, and induces a pulsatile flow that may be beneficial for distal organs. Few published data exist on this aspect; however, Doll and coworkers found a significantly higher survival rate in postcardiotomic ECMO patients in whom an IAB was used [32].

Adequate unloading of the left ventricle must be ensured. This is of paramount importance to prevent LV distention and, in turn, inadequate myocardial rest, elevated filling pressures, pulmonary edema, and respiratory failure that might subsequently compromise weaning from extracorporeal support. Various tools may be used to obtain this. Increasing the pump flow rate may paradoxically worsen the situation, as this leads to a further increase in afterload, while it is unable to drain the bronchial circulation. Low-dose inotropes are often helpful in many patients, as they promote a certain degree of ejection, which is sufficient to prevent LV distension and blood stagnation. Counterpulsation may also provide a certain degree of "external venting" to the LV and be useful in numerous patients. The adequacy of LV unloading should be accurately evaluated throughout the course of extracorporeal assistance, as a direct venting of the left heart may become necessary. This might be accomplished with various techniques, which are presented in a specific chapter. Irrespective of the method used, careful monitoring of the adequacy of unloading is warranted.

9.6.2 Monitoring of Heart and Lung Function

Echocardiography represents a fundamental tool for the daily assessment of the ECMO patient. Its integration with *conventional hemodynamic measurements* allows optimizing and individualizing treatments based on the changing conditions and needs of the patient. Moreover, during the phase of full extracorporeal support, when standard hemodynamic parameters are frequently inconclusive, it gives direct clues on the status of the heart.

Specific aspects of echocardiographic monitoring during ECLS are presented in the relevant chapter.

Chest x-rays and *chest ultrasound* are useful in evaluating the lung to detect pulmonary edema and monitor the appearance of parenchymal consolidations. Besides this, *blood gas analysis* is determinant in estimating the adequacy of the natural lung before weaning from ECLS. Blood should ideally be sampled from a right radial arterial line, as this is the closest sample site to the left ventricle and the less likely to be influenced by extracorporeal flow. It hence represents the closest approximation to blood coming from the natural lung.

Myocardial specific enzymes should be monitored at least on a daily basis during the acute phase to determine the timing of weaning and to detect recurrent ischemia and infarction. Troponins and myocardium-specific isoforms of creatine kinase (CK-MB) are commonly used, while myoglobin is almost constantly elevated due to peripheral muscle release and does not hence represent a reliable index of myocardial ischemia.

Natriuretic peptides are generally extremely elevated upon presentation. Since their half-life is relatively short (the half-life for BNP being shorter than that for NT-proBNP), serial measurements may be of value in guiding the management [33].

9.6.3 Discontinuation of ECLS

In patients presenting with myocardial ischemia, no weaning trial should be attempted before 48 h of ECLS or until a significant reduction in cardiac enzymes is observed.

The suitability for a weaning attempt must be judged based on multiple considerations:

1. Myocardial recovery should be adequate to provide a satisfactory hemodynamic stability without extracorporeal support and with low doses of inotropes. This can be evaluated with a staged “echodynamically” guided reduction in ECMO blood flow.
2. Lung function must be sufficient to ensure acceptable gas exchange after disconnection from ECMO.

3. Complications of ECLS must be accurately investigated and may prompt acceleration in the weaning process.

Weaning from extracorporeal support is attempted in a stepwise fashion as described in the relevant chapter.

Not all patients will succeed their weaning trials.

In such patients, additional factors must be taken into account:

1. Time from initial insult and extension of the affected myocardium. Is a late recovery conceivable? In the majority of patients, most of the myocardial recovery occurs in the first few days after revascularization. However, in some patients, recovery continues for longer periods (weeks or months) [34]. ECMO presents some disadvantages in these patients who need a prolonged assistance: suboptimal LV unloading, increased afterload, low lung perfusion, hemolysis, immobility of the patient, platelet consumption, and thromboembolic events, to name the most relevant. Patients in whom a late recovery is likely may benefit from a VAD as a bridge-to-decision.
2. Organ failures (apart from the heart). What is the neurological status? Lung function? Renal function? GI function? Nutritional status?
3. Presence of sepsis or septic shock.
4. Age and comorbidities.
5. Psychological and psychiatric conditions.

Answers to these questions will determine the suitability for transplantation or long-term VADs implantation (either as a bridge-to-transplant, bridge-to-decision, bridge-to-recovery, or as a destination therapy).

The peculiar aspects of VADs and transplant candidates will be dealt with elsewhere in the book.

9.7 Conclusion

Functional recovery of the heart in the setting of AMI largely depends on the pre-occy and completeness of revascularization.

In patients presenting with refractory CS complicating AMI, a mechanical circulatory support may become necessary to stabilize hemodynamics and prevent irreversible organ dysfunction. In these patients, extracorporeal support must be initiated without delay. ECMO represents an easy-to-implant device; it can be applied with a percutaneous approach virtually everywhere by surgeons or intensivists in a matter of minutes and provides biventricular and respiratory support. Diagnostic and therapeutic procedures are easily performed under stable conditions during ECLS. Patients can be supported with ECMO for a few days or weeks and disconnected when myocardial recovery is adequate, or bridged to long-term VADs or transplantation when indicated.

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Sudden cardiac arrest (CA) is a complex, life-threatening event requiring a multidisciplinary approach. Many strategies have been proposed over time to achieve the return of spontaneous circulation (ROSC) and to optimize post-resuscitation care in order to ultimately improve survival. These include medical, organizational, and technical aspects: mild hypothermia, oxygen control, regionalization to specialized post-resuscitation care centers, and extracorporeal membrane oxygenation (ECMO). In this setting, ECMO might represent a unique resource for highly selected patients suffering from CA in which conventional treatment failed.

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10.1 Sudden Cardiac Arrest: a Multidisciplinary Approach for a Complex Event

Sudden CA is a complex and potentially catastrophic event that was dealt with since 1988 with a multidisciplinary approach that resulted from the famous concept of “life-support chain,” coined by Peter Safar [1]. Although this approach improved the management of CA, its high mortality and morbidity remain a problem to face. CA is a heterogeneous scenario, which can arise from different etiologies, with different electrical rhythms of presentation, rapidly evolve to ROSC or be refractory, and occur in hospital or out of hospital. In this regard, efforts to improve CA survival over time were directed to a broad spectrum of issues including medical, technical, and organizational aspects. Despite this, survival of both in-hospital and out-hospital cardiac arrest (IHCA, OHCA) remains very low. Discouraging results about IHCA survival were largely reported with a survival rate ranging from about 10–22 % [2–4], confirmed by both the BRESUS study [5] and the National Registry of Cardiopulmonary Resuscitation from the United States [2] in which 44 % of 14,720 patients suffering IHCA had ROSC, while only 17 % survived to hospital discharge. As for OHCA, survival rate remains less than 10 %, even if over the past decades efforts have been made to get more adherence to ILCOR guidelines, with the implementation of the chain of survival and providing early CPR and defibrillation with automated external defibrillators by lay bystander and first responders [2, 6]. A systematic review by Sasson et al. [6] analyzed 80 studies involving about 143,000 OHCA of presumed cardiac origin over a period of 30 years and reported a survival rate ranging from 6.7 to 8.4 %, almost unchanged during the three decades. Interestingly, they showed that in witnessed CA, CPR performed early by expert medical or paramedical personnel and presenting shockable rhythms positively impacted survival. Other important factors affecting outcome were early defibrillation [7] and CPR quality [8].

Moreover, it should be underlined that mortality and morbidity after CA are also affected by the so-called post-cardiac arrest syndrome, characterized by anoxic brain injury, myocardial dysfunction, and systemic response to ischemia and reperfusion injury [9]. In fact cerebral ischemia may last for some hours after resuscitation [10], and after ROSC an additional injury occurs due to reperfusion that causes the release of toxic metabolic products.

In this regard, together with efforts aimed at achieving ROSC, over time many strategies for cardiac and neurological protection during resuscitation care have been proposed.

Hypothermia was firstly proposed as a neuroprotective treatment after anoxic brain injury. The mechanisms underlying its beneficial effects on cerebral tissue have already been described [9–13], but hypothermia also has protective effects on myocardial tissue as already shown by experimental studies [14]. A reduction of infarct size has been described, especially when the myocardium is cooled before or at the beginning of reperfusion [11, 12].

The use of moderate hypothermia was firstly reported in the late 1950s and early 1960s, but because of the high rate of complications and inconclusive findings, it was

somehow abandoned until the 1990s, when laboratory studies demonstrated beneficial effects of mild hypothermia in animal models [15], then followed by preliminary clinical studies [16]. Ten years later, two randomized controlled trials from Australia and Europe showed a better neurological outcome in patients suffering from CA due to ventricular fibrillation treated with early mild hypothermia (32–34 °C) for 12 or 24 h [10, 13]. In the European study, a significantly lower mortality in the hypothermic group compared to the normothermic group was also found [13]. However, some limitations of these studies warranted further investigations, especially about the possibility of extending therapeutic hypothermia to CA from non-shockable rhythm in which this therapeutic option is recommended with a low level of evidence (Class IIb) [17] or in IHCA patients [16]. A recent systematic review and meta-analysis [18] evaluated the effects of hypothermia in patients after non-shockable rhythm CA showing that the relative risk of in-hospital mortality was significantly lower in the therapeutic hypothermia group than in the control group, whereas the beneficial effects of hypothermia on neurological outcome appeared less evident.

Another important aspect of resuscitation care is represented by the control of oxygenation during ventilation in patients after ROSC and the subsequent amount of oxygen to brain and tissues. Which concentration of supplemental oxygen should be delivered to patients is actually debated: too little oxygen may amplify anoxic injury; too much oxygen may increase *free-radical* production and lead to cellular injury and apoptosis [19, 20]. Despite previous data suggesting a correlation between hyperoxia and in-hospital mortality in resuscitated patients [19], in Bellomo et al. [21], this association failed. In this regard, due to the uncertainty about the detrimental effects of hyperoxia and the certainty of the potential harmful effects of hypoxia, a revision of the current guidelines targeting an arterial oxygen saturation between 95 and 98 % in these settings seems actually not justified [20, 21].

Since both prehospital interventions and in-hospital post-resuscitation care affect survival in OHCA, it has been proposed to direct comatose patients after OHCA to specialized centers [22]. Better neurological outcomes were described when pre-hospital ROSC patients received specialized post-resuscitation care [23]. In a recent retrospective observational study using a nationwide OHCA registry in South Korea, the benefit of transporting post-ROSC patients toward high-volume centers compared to low-volume centers was demonstrated [24]. Thus, regionalization to specialized post-resuscitation care centers of OHCA patients seems to play an important role in improving survival rate.

Venoarterial extracorporeal membrane oxygenation was introduced as an additional step in the chain of survival for selected RCA patients. Derived from the pioneering applications of heart-lung machines firstly applied in the 1930s by Dr. Gibbon, advances in technology over time allowed a wider and extended use of this unconventional device, leading to progressively more encouraging results [25–28].

In the University Hospital of Caen between 1997 and 2003, 40 patients with refractory IHCA were treated with extracorporeal life support (ECLS); ECMO was discontinued in 22 patients due to brain death or multiorgan failure, 18 patients survived to the first 24 h of support, and 8 patients were alive without any sequelae at 18-month follow-up [3]. Chen et al. [27] obtained slightly better results in a 3-year

prospective observational study about the use of ECLS versus conventional CPR in 92 patients suffering IHCA of cardiac origin. Patients were analyzed by a matching process based on propensity score to equalize potential prognostic factors. Survival rate was significantly higher in the ECLS matched group than in the conventional treatment group at discharge, after 30 days and after 1 year. A few years later, Shin et al. [26] confirmed these results in a retrospective study applying a similar propensity score and reviewing data collected between 2003 and 2009 on 120 IHCA patients. Analyzing 77 patients suffering refractory CA treated with ECLS, Kagawa et al. [29] described a weaning rate from ECLS and 30-day survival higher in the IHCA than in the OHCA group. Similar results were reported from our group [30], suggesting more favorable outcomes with ECLS in IHCA than in OHCA patients.

All these studies suggest the feasibility and the potential benefits of extracorporeal cardiopulmonary resuscitation in patients with CA refractory to conventional treatment.

Thus, ECMO is a strategic option before ROSC because it promptly restores circulation, but it also plays a pivotal role in the post-resuscitation period. In fact, it allows leaving the heart at rest and can promote the return of spontaneous rhythm thanks to its capability to get ventricular unloading and ensure myocardial perfusion. Lin et al. [31] compared patients who had return of spontaneous beating (ROSB) after ECLS with those that had ROSC after conventional CPR: no different survival rate at hospital discharge, after 30 days, 6 months, and 1 year, was found between groups. However, the authors emphasized that ROSB was obtained by ventricular unloading and providing extracorporeal support in patients with ECLS.

Moreover, ECMO provides other advantages, such as the possibility of performing advanced radiologic investigations and definitive surgical or percutaneous treatments in refractory CA of unknown origin, even before an ROSC is obtained [25, 29, 32, 33]; in our ECMO population, 36 OHCA patients and 15 IHCA patients underwent emergency coronary angiography; among these, 25 OHCA and 11 IHCA patients were revascularized percutaneously, while 2 OHCA and 5 IHCA patients were directed to surgical revascularization. Secondly, ECMO could provide rapid cooling and controlled rewarming for therapeutic hypothermia; it can also be applied in medical intoxications [34]. Finally, when cerebral death occurs after CA anoxic injury, ECMO could provide peripheral perfusion to make patients organ donor [25].

Thus, ECMO could be considered as the next link in the chain of survival in selected patients suffering from refractory CA, provided each previous step of resuscitation strategy was promptly performed according to the ILCOR recommendations. At the same time, it could play a pivotal role in the post-resuscitation period too.

10.2 Which Criteria for a Special Unconventional Therapy

Although progressively more encouraging results were described over time from the use of ECMO in refractory CA, criteria for its positioning are still debated. To date, studies failed to provide precise indications and contraindications to ECMO in this setting, while it is fundamental to identify clear criteria to avoid futile treatments.

Refractory CA is usually defined by the lack of ROSC within a period of 30 min of CPR [35, 36].

The first issue that must be considered in the decision whether to consider a patient for ECMO is the “no-flow time” (i.e., the duration of CA without cardiac output before CPR). The duration of no-flow time can be known precisely only in witnessed CAs, and the best candidates to ECMO in this setting are those receiving immediate CPR by bystanders, since the no-flow time is negligible in these patients. Indications about the duration of no-flow time are lacking or inhomogeneous in literature. The French guidelines [36] proposed an algorithm in which no-flow time is matched with the rhythm of presentation. The authors suggested a no-flow time below 5 min as a cutoff for ECMO application when patients are found asystolic, but their algorithm proceeds to the next step (i.e., evaluation of the low-flow time) even when this time is longer than 5 min if the presenting rhythm is different from asystole. Le Guen et al. [25] also suggested a no-flow time below 5 min as an inclusion criterion for ECMO in their OHCA population. The duration of no-flow time may lose its importance when vital signs such as spontaneous movements or spontaneous respirations occur during CPR. Moreover, the role of no-flow time appears less critical during hypothermia because of its protective effects from ischemia on cerebral and cardiac tissues [9–13]. Literature reports longer no-flow times in OHCA than in IHCA patients [30].

The second important factor to assess is the “low-flow time” (i.e., the duration of CA with low cardiac output during CPR). There is no definitive consensus on the optimal low-flow time limit: the shorter the low-flow time, the better the outcome, but its duration varies between authors and also combines with the quality of CPR. Some studies showed a more favorable outcome in patients treated with ECMO after IHCA compared with those after OHCA [29, 30], with longer delays between collapse and the start of ECMO in the latter. Although a cutoff of 30 min to start ECMO has been previously suggested [30], some evidence that ECMO allowed a longer CPR duration than expected in conventional CPR has been described [3, 27, 29, 30, 37]. Massetti et al. reported an average of 72 min of CPR before the onset of ECMO in surviving patients [3]. Chen et al. [37] further extended this time having a probability of survival of about 10 % in patients in which CPR lasted 90 min. Positive outcomes were recently reported in ECMO patients receiving about 138 min of CPR before ECLS [38] and in a subgroup of intoxicated patients alive at 1-year follow-up, in which CPR lasted up to 180 min [32].

The quality of CPR is also a critical issue for neurological outcome, not only the duration. Massetti et al. [3] showed that effectiveness rather than the duration of CPR has to be considered in the decision process. In 2005, Abella et al. [39] analyzed 67 patients undergone CPR after CA and showed that in-hospital CPR was highly variable and not consistent with current guidelines, even if performed by well-trained medical personnel. Similar results come from a study aimed at testing the quality of CPR in 167 patients with OHCA treated by paramedics and nurse anesthetists, where chest compression was too shallow or withheld for half of the time of resuscitation [8]; higher chest compression variability was also found in the prehospital setting as compared to the emergency department [40]. In the

prehospital phase, the introduction of automated chest compression devices may help to overcome the difficulties correlated to CPR during transportation. Despite initial discouraging results, promising data have been reported recently, even if the beneficial impact on survival has not been demonstrated yet. Duchateau et al. [41] showed that in patients with OHCA treated with an automated load-distributing chest compression device, diastolic and mean blood pressure were increased. In a prospective cohort study, 1,011 patients suffering prolonged CA in emergency department were treated with “load distributing band” (LBD) CPR or manual CPR. A higher tendency toward improved survival and neurological outcome at discharge was found in the LBD-CPR group compared to manual CPR group [42].

Finally, an index that indirectly reflects the cardiac output obtained during CPR is the end tidal carbon dioxide (E_tCO_2): an E_tCO_2 below 10 mmHg after 20 min of ACLS maneuvers seems to accurately predict death in CA with electrical activity without pulse [38]. Thus, patients presenting with an E_tCO_2 below 10 mmHg should not be supported with ECLS.

As for exclusion criteria, severe comorbidities precluding ICU admission should be considered as contraindications to ECMO positioning: terminal illness, acute aortic dissection, preexisting irreversible brain damage, hepatic failure, or late stage of respiratory distress syndrome [3, 26, 28–30]. Age alone should not constitute a limitation since it does not appear a sufficient reason to limit ICU admission, although some authors excluded from treatment patients older than 75 years [3, 28].

Finally, the decision to discontinue ECLS support is critical and based on the patient’s clinical evolution: severe neurological impairment up to brain death [3], irreversible multiorgan failure, or intractable sepsis [32] should warrant ECMO discontinuation. However, larger studies are needed to identify negative predictive factors during the clinical course of ECMO.

10.3 Monza’s Flow Chart

Our group in Monza proposed a simple flow chart that could help the attending physician in deciding when and when not to start an ECMO support in case of refractory CA (Fig. 10.1).

We must emphasize that this flow chart only represents a recommendation, since it is the attending physician’s responsibility to decide whether to initiate ECLS, even in the presence of prolonged no- or low-flow time, based on clinical or anamnestic factors, e.g., the appearance of vital signs, or a good CPR performed by well-trained personnel or with an automated chest compression device.

The first point to assess in our flow chart is the presence of comorbidities precluding ECMO positioning as reported below (Fig. 10.1).

We decided to use a no-flow time of 6 min and a low-flow time of 45 min on the basis of the literature and from our preliminary results [30]. To reduce the no-flow

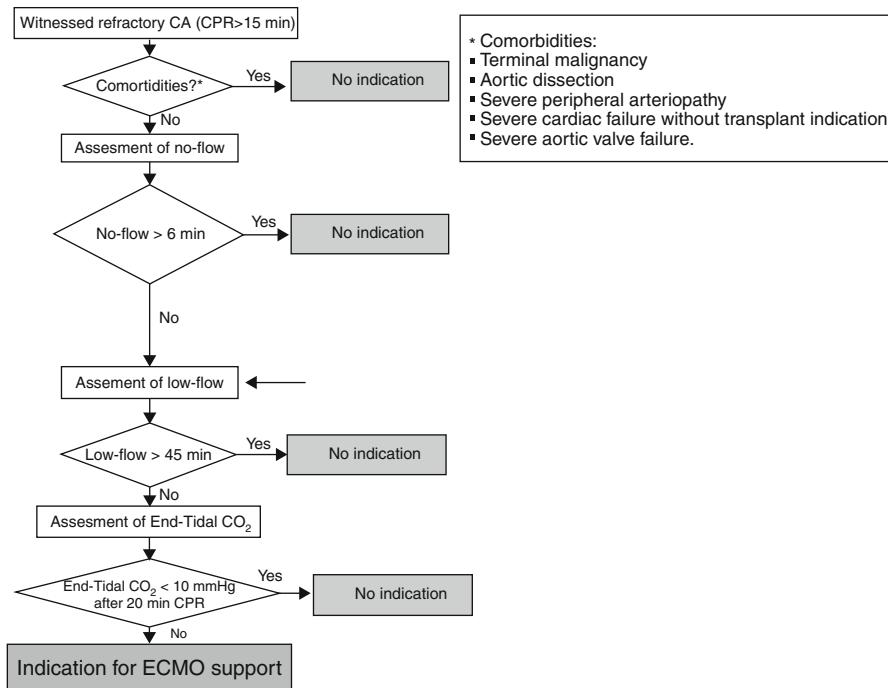


Fig. 10.1 Monza's flow chart for ECMO support in refractory CA

time, we promoted telephone-guided CPR performed by bystanders. To reduce the no-flow time, our ECMO team was alerted for all CA patients when ongoing CPR lasted more than 15 min. In OHCA, the ambulance crew was prompted to leave the scene and begin transport after no more than 15 min of ACLS maneuvers in the absence of an ROSC, to reduce the no-flow time to a minimum.

Finally, an E_tCO_2 below 10 mmHg measured after 20 min of CPR contraindicated ECMO.

10.4 Conclusion

Sudden CA is a complex event with high mortality rate. We strongly believe that optimal state-of-the-art conventional treatment should constitute the basis for every CA patient. ECLS represents a valuable additional therapeutic option both in achieving ROSC and in post-resuscitation care in highly selected CA patients not responding to the conventional approach.

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11.1 Definition of Postcardiotomic Shock

The definition of postcardiotomic circulatory shock (PCCS) is still not unique in literature, but probably the most accepted reflects patients who have inadequate cardiac performance after cardiac surgery despite inotropic and intra-aortic balloon pump (IABP) support. This uncommon but serious complication has been reported to occur in approximately 0.2–6 % of adult patients undergoing cardiac surgical procedure [1, 2]. As defined by Rao et al. [3], PCCS includes not only the patients who cannot be weaned from cardiopulmonary bypass in the operating room but also those who show “low cardiac output syndrome” (LCOS) in the early postoperative period. Thus, PCCS may be identified as a type of LCOS after cardiac surgery causing inadequate end-organ perfusion despite maximal medical support.

11.2 Indications and Timing for Mechanical Cardiac Support

Regardless of the definition, PCCS is a clinical condition associated with an extremely poor prognosis, with a mortality rate greater than 70 %. It increases over 85 % when three of high-dose inotropes are needed to separate from CPB [4]. Therefore, in the absence of clinical improvement despite maximal inotropic support, the benefit-risk ratio shifts in favor of mechanical cardiac supports (MCS).

The MCS is intended to bridge the patient to recover or, if it is not possible, for transplantation or evaluation of alternative strategies.

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Different types of MCS systems are currently available to treat PCCS [5–9]. They include simple centrifugal pumps implanted as left ventricular assist systems [10, 11] and complex and expensive ventricular assist devices (VAD) [5].

The results of these different experiences with different devices are not comparable coming usually from limited, monocentric, and retrospectively collected data [6, 8, 11]. Nevertheless, the uncertainty of recovery and often the lack of alternatives to it have led the clinicians to opt for “bridge to decision” solutions at low cost. The use of extracorporeal membrane oxygenation (ECMO), namely, a circuit with an oxygenator in addition to a centrifugal pump, has gradually increased over time for its simplicity, ductility, reliability, and limited costs [2, 12, 13].

Only venous-arterial VA ECMO can support both lung and heart function and allows further evaluations at low cost when the underlying reason of postcardiotomic shock has not yet been fully clarified.

Several published experiences have underlined the capital importance of early implants to avoid suboptimal perfusion, leading to MOSF, to increase the weaning rate and to improve the outcome [3, 4, 11].

The ECMO support is contraindicated when the patient's life expectancy is deemed poor and unlikely to be improved by MCS (i.e., terminal illnesses, irreversible neurological injury, advanced MOF). Technical contraindications include aortic dissection and severe aortic regurgitation [14].

11.3 Options and Modalities of Support

ECMO for PCCS opens several possibilities of action, being not a device, but a system. Different cannulation sites allowing diverse configurations (central, peripheral, or “mixed”) can be employed for ECMO institution. Having distinctive physiology, characteristics, and issues, these should be selected on the basis of the specific patient's needs and features.

The central cannulation (i.e., inlet in the left and right atria and outlet in the aorta) is perhaps the easiest to adopt in the operating theater and probably the most physiological. It allows real biventricular unloading, lower shear stress (shorter and bigger cannulae), higher flow rates, and a simple upgrade to medium-long-term ventricular assist devices in comparison to the peripheral one. The main concerns are the risk of infection, hemorrhage, and the need of sternotomy to remove it.

The peripheral cannulation (i.e., inlet and outlet in large peripheral vessels) is simpler, is associated with lower bleeding risks, and can be performed quickly with percutaneous technique in emergency condition. Lastly, it does not require re-sternotomy. However, it supports only the right ventricle and it may be associated with left ventricular distension, leading to increased myocardial VO_2 , wall tension, and eventually myocardial ischemia. The latter can adversely affect myocardial recovery and result in pulmonary edema. Several options have been suggested to solve this problem due to the countercurrent flow of the pump.

The first option is the inotropic support, but it increases the myocardial oxygen demand, interferes with the recovery, and increases the risk of malignant arrhythmias.

The use of IABP decreases the left ventricular afterload and increases the coronary perfusion pressure during diastolic time. This appears to be extremely relevant in a patient with peripheral cannulation, in whom an increased left intraventricular pressure can occur [15].

However, only venting the left heart may decrease the ventricular pressure and really unload the ventricle. To get this goal without sternotomy, several alternatives have been proposed. Some authors privilege a transseptal left atrial cannulation [16, 17]. Others create an atrial septal defect by a percutaneous blade or by balloon septostomy [18]. Others prefer a transaortic vent through the aortic valve [19] or associate ECMO to Impella [20]; others use a large pulmonary catheter as a vent [21].

Other complications of peripheral cannulation include the so-called harlequin syndrome, the leg ischemia, and the formation of thrombi in the ascending aorta during total extracorporeal support [22].

The harlequin syndrome comes from the competition between the output of the recovering heart and the ECMO flow, when the pulmonary function is impaired. The upper part of the body, depending on the native lung, will be hypoxic and cyanotic (“blue head”), while the lower part of the body will be well oxygenated (“red leg”). Therefore, certain key organs, such as the brain and heart, may be compromised for local differences of flow distribution.

The acute leg ischemia may be prevented by inserting a catheter into the femoral artery, just distally to the ECMO cannula, and connecting it to the ECMO outlet to provide the distal perfusion.

The use of near-infrared spectroscopy (NIRS) during ECMO support has been recently advocated [23]. It allows early detection of regional reduction of perfusion in the development of a compartmental syndrome or neurological complications [23]. Stressing that in this patient the risk of neurological injury is high (7–50 % of the patients [24, 25]) and the difficulty to determine the neurological status of an intubated, and often heavily sedated (if not paralyzed), patient.

Thrombosis of the ascending aorta is another rare complication of venous-arterial ECMO via femoral artery. It is due to minimal left ventricular ejection and stagnant flow in the aortic root.

The direct trans-apical cannulation of the left ventricle is another type of cannulation that overcomes, through a left thoracotomy, the problem of the left ventricular distension [26]. This modality, often used for VAD implantation, ensures the best ventricular unloading. It avoids the sternotomy, usually considered more invasive and a source of greater surgical complexity in case of transplantation. Moreover, it allows, when the right heart recovers, to convert a partial peripheral ECMO to a midterm LVAS, by simply removing the venous femoral cannulation and the oxygenator [26]. It is not more traumatic than the atrial one and may be removed without implications for the ventricular function.

The axillary artery can replace the femoral artery as the site of arterial cannulation; usually a Gore-Tex graft is end-to-side anastomosed to the axillary artery, connected to the arterial cannula, and tunneled subcutaneously to prevent infection [27]. This cannulation reduces significantly the afterload and avoids harlequin syndrome and thrombosis of the ascending aorta.

11.4 Management

Several preoperative risk factors of LCOS have been identified both in coronary and in valve surgery [3, 28]. Risk stratification is useful to select patients and to provide for assessment eligibility to VAD or transplantation, as well as to plan the surgical procedures (preoperative vascular assessment, right radial artery placement, Scarpa's triangle, and the subclavian artery free from surgical drape, etc.).

A pulmonary-artery catheter should be positioned at the induction of the anesthesia, because its positioning after central cannulation (but often after peripheral) may be problematic, even under fluoroscopic guidance. It may help during the weaning of CPB and the management of ECMO. At some centers the left atrial pressure is monitored with a catheter that may also be used to evaluate the pulmonary gas exchange during the weaning phase.

When the inability to wean the patient from CPB becomes evident, a MCS system must be chosen without wasting time and struggling with the hemodynamic.

If only the left heart is involved, several devices are to be considered (Impella, CentriMag, Abiomed, TandemHeart, LVAD, etc.), but the discussion is beyond the scope of this chapter.

If the failure involves only the right ventricle, a centrifugal pump with inlet in the right atrium and outlet in the pulmonary artery may be used, but even if the right atrium is drained, the increase of the afterload induced by the pump can seriously affect a ventricle, physiologically accustomed to working against low pressure. Therefore, the development of tricuspid regurgitation, as adaptive response, is common. In addition, the management may be very difficult if a left diastolic failure is present.

In comparison the VA ECMO provides a complete unloading even with peripheral cannulation, but, shunting the pulmonary circulation; it needs the addition of an oxygenator to the circuit.

However, a biventricular failure is often present, often associated with a severe gas exchange impairment. In these cases, the use of VA ECMO is valuable. When in doubt, supporting the right heart may be the right choice, since a right ventricular failure can be swift and fatal.

In this case, since the sternum is already open, surgeons usually prefer the central cannulation for the VA ECMO, but there are conflicting opinions, as previously described (need of redo sternotomy and bleeding).

At our center we usually choose the central cannulation, from the left and right atria to the aorta, because the better unloading of the left ventricle ensures a higher probability of weaning. The peripheral cannulation is reserved to a patient with isolated right ventricular failure, after heart transplantation or pulmonary endarterectomy. The peripheral one is preferred also in acute heart failure that occurred in the ICU; it allows solving the dramatic situation, permitting to save the patient and, afterward, if necessary, easy transfer to the operating room to convert it to the central one.

Echocardiography plays a key role in the decision-making and in the whole ECMO management: firstly, in evaluating the right and left ventricular function [29]

and then in disclosing contraindications to implant, such as aortic valve insufficiency, or abnormalities can affect the function or position of the cannula (PFO, septal aneurism, tricuspid pathology, etc.). It is useful for detecting complications such as cannula malposition, displacement, or obstruction; pericardial effusion; cardiac tamponade, thrombosis; or aortic distortion.

Another challenge in the OR is understanding if the right ventricle is able to tolerate LVAS, or biventricular support is needed, because the pre- and afterload can change easily and quickly. Several echocardiographic parameters predictive of an RV dysfunction after VAD implants have been described, but they have been validated only in elective conditions [30, 31].

The echocardiography can also guide the setting of the mechanical ventilation, minimizing its effect on the right cardiac function and its influence, as confounding factor, on the comprehensive assessment [32] or on weaning attempts.

The balance between the cardiac output of the native heart and the outflow of the ECMO is not only the key element of hemodynamic management but also the first step to prevent the left ventricle distension with peripheral support. The goal is maintaining ventricular ejection and evident pulsatility on arterial pressure monitoring, to avoid the complications previously described, even at the cost of a significant inotropic support.

Nevertheless, the sum of the ECMO flow and the cardiac output must keep the peripheral perfusion normal and sustain the metabolic needs of the different parenchymas.

The anticoagulation should be increased and the afterload decreased, reducing pump flows and using inodilators judiciously, even though maintaining the left ventricular ejection may be impossible if the ventricular function is severely depressed.

In that case, if ventricular distension develops, the left ventricle must be drained.

Another important goal is to maintain an effective perfusion pressure. Vasoconstrictor drugs are often needed, above all, in case of long-lasting CPB or late implant. Often the autoregulatory mechanism of the kidney perfusion is lost, and the development of acute kidney injury is frequent. It is to emphasize that AKI is an independent risk factor of poor prognosis and can prevent the entry into a transplant/VAD program [33, 34].

The onset of sepsis is a further condition that not only worsens the prognosis but contraindicates the transplant. Only a diligent management of cannulae and devices, a strict clinical and microbiologic monitoring, and the use of antibiotics in an early, appropriate, and limited time span can reduce the probability of infection in such high-risk patients.

At our institution, usually, the patient is extubated as soon as possible to prevent pulmonary complications. The weaning from ventilator is assisted by ECMO, but all contraindications to extubation, especially the neurological ones, must be absent.

The patient should be able to expectorate, to eat, and to collaborate with nursing. The central cannulation allows good comfort for the patient and fair mobility.

An acceptable respiratory exchange should be reached even in the centrally cannulated patient, because the coronary flow is preferably supported by blood oxygenated through the natural way [35].

Contrary to the VV ECMO, the respiratory exchange after the weaning from the assistance is not easy to predict with a VA ECMO, and then its removal can compromise the residual respiratory function.

Moreover, weaning the patient from ECMO and then keeping him/her sedated, intubated, ventilated, and on high inotropic support has little meaning, and it could go against the philosophy of the system and the weaning. As an intermediate step, medium inotropic support and noninvasive ventilation can be used.

Thus, early extubation, if viable, simplifies the medical and nursing care, decreases the risk of infection and allows to place the patient in conditions that help to understand who is really weanable or who should be quickly managed with different strategies (OHTx or VAD).

11.4.1 Anticoagulation

The principal causes of ECMO mortality and morbidity are bleeding and thrombosis [36]. Taking the utmost care is required for hemostasis not only of the surgical field but also of the cannulation site.

A bleeding tendency may persist for several hours, usually until the day after, meaning that the hemostatic status should be frequently assessed. The heparin-infusion at low dose, essential also with the heparin-coated circuits, should be initiated, as soon as the coagulation system starts to recover, to avoid platelet consumption and dangerous thrombocytopenia.

Viscoelastic tests (TEG or ROTEM) have the advantage to give information not only about the initiation of clotting but also about the strength and dissolution of the clot [36]. These point-of-care tests may monitor this change: the heparin infusion should be managed comparing TEG to TEG with heparinase and looking at the PTT ratio, because the ACT, even if widely used, does not correlate with heparin levels [37]. The goal is PTT about 1.5–2.5 normal and an r time greater than 60'', but it depends on the ongoing coagulation profile, the platelet number/function, and TEG signs of hypercoagulability.

The use of direct thrombin inhibitors and the like has been advocated, but this is accepted worldwide only as a therapy of HIT type 2 for costs, pharmacokinetic/dynamic reasons, and absence of antagonists [38].

11.4.2 Weaning

Several protocols have been proposed for the withdrawal of ECMO, but every patient is a particular case with its history, original pathology, and hemodynamic, and ventilator status. Nevertheless, the ECMO flow must be reduced gradually, looking carefully at the symptoms and signs of unsuccessful weaning. Singular care must be taken to obtain a sufficient heparinization at low ECMO flow.

Usually the echocardiography and the Swan-Ganz catheter monitor the cardio-circulatory response, but a comprehensive evaluation of the patient is capital. A

small decrease of urinary output; a trivial increase of central temperature with pale, cold skin; a little change of the respiratory frequency; or a slight alteration of the neuropsychological status may be the first signs of an impossible weaning.

Looking at the trend of lactates, diastolic pulmonary arterial pressure, and obviously SvO_2 is useful to predict how the attempt is proceeding. Some echocardiographic parameters at ECMO flow of 1 L/min may predict a successful weaning, as the aortic time-velocity integral ≥ 10 cm, the ejection fraction $>20\%$, and lateral mitral annulus peak systolic velocity ≥ 6 cm/s [39].

Another issue that can prevent the weaning from ECMO is the respiratory gas exchange. During the ECMO support, different lung injuries may determine a hypoxic state that hampers the weaning. In that case many authors advise the conversion to a venous-venous ECMO if the heart function is satisfactory.

11.4.3 Outcome

Several risk factors have been reported as independently related to poor outcome of PCCS: prior cardiac arrest followed by severe cardiogenic shock [6], age, base deficit, and emergency [8, 40]. As outlined by Rao, all are probably linked to a delay in implant [41].

Significant predictors for death after VA ECMO include previous cardiac surgery, older age, thoracic aortic surgery, and nonuse of IABP [1]. The advanced age alone is not an absolute contraindication [42], but Rastan et al. [2] confirms that age older than 70 years, obesity, and diabetes are independent risk factors for in-hospital mortality.

The underlying cardiac disease and the related surgery had a significant effect on hospital survival: CABG had better prognosis (in-hospital survival of 44 %) than mitral valve surgery, but the worst was for aortic arch and pericardectomy, probably due to bleeding complications. The prognosis for patients with ECMO after type A dissection, constrictive pericarditis, or double valve disease is extremely poor. The pre-ECMO lactate values are strongly associated with increased hospital mortality [2].

Predictors for in-hospital mortality during ECMO are acute liver and renal failure [43] and persistent high lactate values, despite a whole mechanical support. Acute myocardial ischemia is an additional adverse prognostic factor, with a close correlation between a high release of creatine kinase MB during ECMO and in-hospital mortality [44]. ECMO is also associated with various and important morbidities.

Severe hemorrhage is the more frequent and challenging complication, leading to reoperation and massive transfusion. The incidence of cerebrovascular events ranges from 17.4 % [2] to 33 % [1] and is a serious complication that may preclude further treatment. Limb ischemia on the side of the femoral artery cannulation is a frequent complication (19.9 %) [1, 43].

The successful weaning rate of ECMO for PCCS ranges from 31 to 60 %, but the in-hospital mortality rate is 59–84 % [2, 13]. This high gap is probably related to the lack of alternatives to weaning in patients who cannot undergo VAD or OHTx and to the complications of treatment that increase exponentially with time.

The ECMO technology has been greatly improved over the last decade, but these changes do not seem to affect major outcomes. A retrospective analysis, comparing three little groups, did not find any differences in renal failure, strokes, or mortality, but showed a statistically significant trend towards reexploration for new systems [45]. Other authors reported a lesser rate of complications, i.e., hemolysis, reduced thrombi formation, and greater interval between oxygenator changes, as shown by Yu et al. [46]. Therefore, technological advancements seem to facilitate patient care and bleeding control more than to reducing main complications or mortality, the latter resulting mostly from comorbidities, initial cardiac injury, and suitability for VAD or OHTx. No less important is the delay in instituting mechanical support.

11.5 Summary

Several devices have been used to support the vital organs in case of postcardiotoxic shock. The supremacy of a system has never been proved, but the VA ECMO is being increasingly used for its simplicity, ductility, and affordability. The PCCS has still a poor prognosis, but early ECMO insertion minimizes the complications of a prolonged CPB and a high inotropic support and seems to be able to increase the survival rate. Several different configurations (central or peripheral cannulation; different cannulae, tubes, and centrifugal pumps) are possible, making the ECMO not simply a device, but a strategy, customizable on the patient's anatomy and needs. Nevertheless, the purpose of insertion is always the same, to earn time: time for recovery, time for transplant or VAD, or time to decide. The outcome depends mainly on the possibilities that may open.

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12.1 Introduction

Myocarditis is an inflammatory condition of the heart muscle, mostly affecting young individuals without significant comorbidities. Its unpredictable clinical presentation and evolution to life-threatening arrhythmias and overt cardiogenic shock explains the major role of left ventricular (LV) mechanical support in affecting short- and long-term prognosis. Though representing a minority of overall indications to ECMO, myocarditis is frequently reported in literature in numerous case reports, case series, and clinical trials, as a group of diseases that offers a wide spectrum of applications for mechanical support for the failing heart. We will review the main features of this group and some rare cardiomyopathies, especially focusing on peculiar aspects regarding ECMO support.

12.2 Epidemiology

The true incidence and prevalence of myocarditis in general population is unknown, mostly because reaching a definitive diagnosis might be challenging, due to the lack of a well-established “gold-standard” noninvasive test and to the low sensitivity of endomyocardial biopsy (EMB). Dallas criteria applied to conventional histology yield a diagnosis only in 35 % of cases [1], and although multiple sampling [1], immunohistochemical analysis [2], and viral polymerase chain reaction (PCR) have yielded higher sensitivity [3, 4], definitive myocarditis can still be diagnosed in only 64 % of patients [5]. Incidence of myocarditis is about 3.5–6 % in different study populations, including both cardiac and noncardiac deaths [6–8]. Similarly, the

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prevalence of myocarditis in idiopathic dilative cardiomyopathy (DCM) population is 9–10 %, often derived from postmortem analysis [9].

12.3 Etiology and Pathogenesis

Etiology of myocarditis is classically divided into infectious causes, in which viral myocarditis represents, by far, the most common isolated species of pathogens and noninfectious causes, represented by a fairly heterogeneous group of diseases (Table 12.1).

Table 12.1 Etiology of myocarditis

Infectious causes	Tests and clues
<i>Viral</i>	
Adenovirus, Coxsackie A and B, echoviruses, parvovirus B19, influenza A and B, herpes simplex, Epstein-Barr, cytomegalovirus, varicella zoster, respiratory syncytial virus, HIV, hepatitis B and C, polio and non-polio enteroviruses, rubella, rubella, mumps, variola, rabies, arbovirus, dengue, yellow fever	Viral cultures and titers Swabs of rectal and nasal mucosa Acute and convalescent antibody titers
Vaccinia (smallpox vaccine)	History of recent vaccination
<i>Bacteria</i>	
Diphtheria, TB, <i>Salmonella</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> spp., <i>Neisseria</i> spp., <i>Clostridium</i> spp., <i>Brucella</i> , <i>Chlamydia</i> spp., <i>Legionella</i> , <i>Haemophilus</i> , cholera, <i>Mycoplasma</i>	Bacterial cultures Early antigens (if available)
<i>Fungal</i>	
<i>Candida</i> spp., <i>Histoplasma</i> , Coccidiomycetes, <i>Aspergillus</i> , <i>Blastomyces</i> , <i>Cryptococcus</i>	Beta-D-glucan Galactomannan antigen
<i>Others</i>	
Spirochetal (syphilis, leptospirosis, Lyme) Rickettsial (typhus, Rocky mountain spotted fever, Q fever) Protozoal (Toxoplasma, amebiasis, malaria, leishmaniasis, trypanosomiasis) Helmintic (echinococcosis, trichinosis, schistosomiasis, ascariasis, filariasis, paragonimiasis, strongyloidiasis)	Careful and detailed history (travel, exposure, tick bite, etc.) and physical exam
<i>Noninfectious causes</i>	
Drug induced (direct toxicity): cocaine, alcohol, catecholamines, arsenic, lead, cyclophosphamide, daunorubicin, Adriamycin	Careful and detailed history and physical exam
Drug induced (hypersensitivity): methyldopa, hydrochlorothiazide, ampicillin, furosemide, digoxin, tetracycline, aminophylline, phenytoin, benzodiazepines, and tricyclic antidepressants	Toxicologic panels
Environmental exposure: snake, scorpion, spider, or insect bites	Drug dosage and ethanol levels
Collagen-vascular diseases: systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, dermatomyositis/polymyositis (sarcoidosis, celiac disease, etc.)	Autoimmune workup
Radiation exposure	Thyroid function and urinary catecholamines
Various: giant cell myocarditis, sarcoid, peripartum, thyrotoxicosis, pheochromocytoma, celiac disease	

Bowles et al. published a large interesting study, defining the most common viral etiology by age group [1]. Besides more common viruses, we also mention myocarditis in HIV-positive patients (for either potential toxicity of gp120 protein or adverse reaction to antiviral agents or to opportunistic infections), in which, although uncommon, it is associated with advanced disease and poor prognosis [10]; 0.01–3 % incidence rates of vaccinia-associated myopericarditis are estimated, occurring within 30 days after smallpox vaccination [11, 12]; and finally, patients with endoscopically proven celiac disease may present a form of virus-negative myocarditis, showing higher titer of serum anti-heart antibodies than general population (4.8 % vs. 0.3 % in control group), presenting with severely depressed ejection fraction (EF) and high NYHA class or ventricular arrhythmias, improved by a gluten-free diet [13].

Pathogenesis of myocarditis is still largely unexplained. From experimental studies in animal models and human population, it was demonstrated that cardiac injury depends on direct viral damage, often requiring expression of surface receptors, and on humoral and cellular host immune response, especially to persistence and replication of viral genome within myocardial tissue [14]. In fact this is associated with a progressive impairment of LVEF and incomplete functional recovery [4, 15], whereas spontaneous viral elimination is associated with a significant improvement in LV function. It is now accepted that individual susceptibility together with stronger native immunity is able to affect both the initial inflammatory response (resulting in shorter duration of severe symptoms) and long-term prognosis (lower rate of progression to DCM) [15]. Autoimmune mechanisms have also been suggested to explain virus-negative myocarditis. In conclusion, initial immune response limits the extent of early viremia, therefore protecting against myocarditis, but once the cardiac damage ensues, the persistence of viral genome can trigger autoimmune response. Noninfectious causes of myocarditis are summarized in Table 12.1.

12.3.1 Hypersensitivity and Eosinophilic Myocarditis

HSM is a drug-mediated autoimmune reaction toward the cardiac muscle, characterized by signs and symptoms of hypersensitivity (skin rash, fever, eosinophilia, and malaise) and nonspecific ECG findings that may occur not necessarily early in the course of drug use (up to 2 years from initial drug assumption). Burke et al. analyzed postmortem histologic samples of patients with HSM to describe histologic findings, patterns of distribution of cellular infiltrates, drug associations, and clinical-histologic correlation [16]: HSM is defined by the infiltration of eosinophils, lymphocytes, and histiocytes in the absence of fibrosis or granulation tissue. Involvement of myocardium is often focal and may be missed in up to 50 % of EMB. The right ventricle (RV) was involved in the majority of patients. Cardiac arrhythmias or unexplained death occurred in 29 of 69 patients, and even worse prognosis was reported by Fenoglio et al. (20 sudden cardiac deaths in 24 patients) [17]. The differential diagnosis with GCM or necrotizing eosinophilic myocarditis can be made only by EMB, but it is crucial for possible treatment; therefore,

accompanying symptoms should be carefully sought. Necrotizing eosinophilic myocarditis associated with the hypereosinophilic syndrome typically evolves over weeks to months, presenting with biventricular failure or arrhythmias, including sudden cardiac deaths (SCD). It has an exceptionally poor prognosis with most cases diagnosed at autopsy.

12.3.2 Giant Cell Myocarditis

GCM is a rare form of autoimmune myocarditis, of unknown pathogenesis, characterized by fulminant course, and grave prognosis, despite best medical treatment. It was previously described only in postmortem samples or explanted hearts. More recently, a multicenter international registry described 63 patients who had a transplant-free survival of 5.5 months without immunosuppressive treatment [18]. Cooper et al. enrolled 11 patients with histologically confirmed GCM, reporting that treatment with steroids, cyclosporine, and monoclonal antilymphocyte antibodies improves long-term survival [19]. A relapse of the disease is described after acute discontinuation of treatment, confirming previously reported findings of histologic recurrence, in posttransplant follow-up EMB. It usually presents with acute deterioration in LVEF, ventricular arrhythmias, and heart block.

12.3.3 Peripartum Cardiomyopathies (PP-CMP)

PP-CMP is rare dilative CMP of unknown etiology affecting women in the last month of pregnancy or within 5 months from delivery, although similar dilative CMP has been described also earlier in pregnancy. It presents with profound cardiogenic shock and major arrhythmias, in young healthy patients, without cardiac or extra-cardiac comorbidities. Although prone to spontaneous recovery, it may present with severe LV dysfunction, mandating prompt mechanical support, and, like acute myocarditis, progresses to dilative CMP, requiring VAD or heart transplantation, despite the best medical treatment. Maternal mortality rate reaches 25–50 %. In literature, several case reports advocate the use of ECMO to allow recovery or to bridge the patients to VAD or transplantation. We report Gavaert et al.'s work describing a 10-year experience with 6 patients affected by PP-CMP, all supported by IABP, 1 by ECMO, 4 implanted with an LVAD, 2 of which were transplanted, and the last being still on list at time of publication. EMB were performed in 2 patients at the time of VAD implant [20].

12.3.4 Catecholamine-Induced and Takotsubo Cardiomyopathies

Pheochromocytoma is a catecholamine-secreting tumor. It originates from the chromaffin cells in the adrenal medulla or in extra-adrenal paragangliomas. It presents with a variety of symptoms, but although catecholamine-induced CMP is a

well-known entity, it presents usually with more benign features and more rarely with unexplained or intractable cardiogenic shock due to paroxysmal release of catecholamines. Grinda et al. described the first case report of successful use of VAD to rescue catecholamine-induced CMP. Huang et al. reported a case series of 3 patients, rescued with venoarterial peripherally inserted ECMO, two of which were under CPR [21]. Literature offers several case reports of centrally [22] and peripherally [23, 24] inserted ECMO and VAD [25]. Septostomy was performed in some cases to decompress the LV. Functional recovery usually occurs within the first few days allowing for further diagnosis and surgical treatment of underlying disease. Interestingly, Sheinberg et al. reported a Takotsubo (apical ballooning appearance of LV) in a pheochromocytoma, successfully rescued by venoarterial ECMO and IABP [23].

12.3.5 Hantavirus Cardiopulmonary Syndrome

Andes virus, Bayou virus, Black Creek Canal virus, Choclo virus, Juquitiba virus, Laguna Negra virus, and Sin Nombre virus, first isolated in the Four Corners region of southwestern, USA, are the etiologic agents of an acute cardiac and respiratory failure called Hantavirus cardiopulmonary syndrome (HCPS), causing deaths (43–76 % of patients) mostly due to multiorgan failure, secondary to intractable cardiogenic shock. Currently, no etiologic treatment is available, and therapy is primarily supportive. Wernly et al. report a two thirds survival and complete recovery of 51 HCPS patients with a predicted mortality of 100 % [26], rescued by venoarterial percutaneous femoral ECMO. Dietl et al reported 38 patients with severe HCPS with similar technique. ECMO had a mean duration of 132 h. Several reports are available in literature [27].

12.4 Clinical Presentation

The extreme variability of histologic patterns (i.e., focality of infiltration vs. diffuse biventricular injury) together with innate immune response could significantly affect the presentation and course of the disease, accounting for a multiplicity of clinical patterns. The majority of patients present with a nonspecific prodrome, mostly confined to respiratory and/or gastrointestinal systems, subsequently progressing in overt although still aspecific cardiac involvement. Clinical features of myocarditis are summarized in Table 12.2. Myocarditis is a major cause of DCM, presenting with classical symptoms of heart failure (HF), with atrial and ventricular arrhythmias, usually manageable with standard of treatment. Conduction delay is more common with infiltrative and GCM than with lymphocytic. Myocarditis represents a cause of SCD without structural abnormalities in up to 20 % of cases [28, 29], in young subjects with little or no prodrome and regardless activity or rest. Only a minority of patients were reported to have SCD during physical or emotional stress [28]. Important to mention, even asymptomatic patients are at risk for SCD. Fulminant myocarditis is well characterized by viral prodrome, acute onset, severe

Table 12.2 Clinical presentation of myocarditis

Aspecific	1. Gastrointestinal: nausea and vomiting, cramp, diarrhea, appetite loss, abdominal and epigastric pain 2. Respiratory: cough, pharyngeal pain 3. General: increased fever, general fatigue, arthralgia and myalgia, headache, and back pain
Cardiac	1. Chest pain or discomfort (particularly common in young patients with coronary vasospasm), concomitant pericarditis, syncope, palpitations, dyspnea 2. Heart failure: generalized fatigue, intolerance to exercise and dyspnea. Subsequently acute or fulminant cardiogenic shock 3. Sinus tachycardia (most common, especially out of proportion with concomitant fever), premature atrial and ventricular contraction, atrial fibrillation, and ventricular tachycardia. I and II degree, up to complete AV block (more common with infiltrative and GCM), RBBB, and LBBB

cardiovascular compromise, and ventricular dysfunction that either resolves spontaneously or rapidly evolves to a fatal course. Acute myocarditis develops ventricular dysfunction that usually progresses toward DCM. Failure of standard of treatment for congestive HF, refractory arrhythmias, and cardiac arrest is therefore the major indication to LV mechanical support, to bridge the patient to full recovery, or to further support (heart transplantation or long-term support devices) in selected cases with otherwise extremely high mortality over the course of a few days.

12.5 Diagnosis

As previously discussed, diagnostic process in myocarditis is complex and articulated. It is based on standard screening routine but also on specific biomarkers and invasive tests. The primary goals in approaching this disease are to select patients who will candidate for further testing; to reach a definitive diagnosis, but also to anticipate, compatibly with the clinical scenario which patients may require LV mechanical support; and possibly to estimate the best option and the likelihood of progression to intermediate-term assist devices and/or transplantation. A thorough discussion of available diagnostic tests and their role in myocarditis is beyond the aim of this chapter. Nonetheless, we will report the most relevant features, and we grouped diagnostic tests for each specific category, in the purpose to offer an extremely practical approach in more emergent situations (Table 12.1). Myocarditis requires a high index of suspicion and should be considered whenever a patient (primarily young males, with gastrointestinal and respiratory prodrome) presents with new onset of unexplained cardiovascular abnormalities. Valvular, congenital, ischemic, toxic (especially ethanol and cocaine related), and pulmonary heart disease should be carefully sought and excluded, before establishing a diagnosis of myocarditis. Concomitant symptoms, such as exanthematous disease, specific pathogen-related symptoms, co-existent pericarditis, or a triad of eosinophilia, rash, and exposure to either a new drug or vaccine, may reveal useful to further restrict differential diagnosis. Therefore, careful and thorough history and physical examination are essential and may help in selecting more focused testing. Some features

Table 12.3 Diagnostic tests results in myocarditis

Diagnostic test	Common features
Chest radiography	Cardiomegaly, pulmonary vascular congestion, and/or pleural effusion (depending on right ventricular and tricuspid valve dysfunction). No specific abnormalities
ECG	Completely normal or with minor, aspecific abnormalities to markedly abnormal Brady- and tachyarrhythmias, conduction abnormalities, ST and T wave alterations, abnormal Q wave, low voltage, and poor R wave progression. Patterns of infarction or pericarditis. Presence of Q wave associated with a severe course, higher early cardiac enzymes, worse LV function, and higher incidence of cardiogenic shock, but not necessarily with a worse long-term outcome (31)
Cardiac enzymes	CPK MB, TnT, and TnI may be elevated (reflecting the extent of myocardial injury). TnI probably superior to CPK MB early in the disease, TnT levels correlating with more extensive damage
Echocardiography	Highly variable, from a completely normal to a markedly abnormal Various degrees of hypokinesis most commonly (mild hypokinesis limited to areas of focal infiltration, segmental wall motion abnormalities or diffuse involvement, with severe hypokinesis) LVEF or FS reduced, not necessarily with LV dilatation
Magnetic resonance imaging	Areas of inflammation and infiltration, mostly focal within the first 2 weeks, more diffuse within 4 weeks. Extent of the lesion correlates with LV dysfunction
Endomyocardial biopsy	5–10 samples from RV septum. Submit 4–5 to light microscopic examination. Transmission electron microscopy may be useful but reserved to infiltrative disorders Routine viral genome testing only for referral centers Several patterns of infiltration (histiocytic and mononuclear), varying in severity and structural abnormalities of myocardium

of routine test may be helpful in suggesting myocarditis (Table 12.3), but they are usually non-conclusive.

12.5.1 Chest Radiography, ECG, and Laboratory Tests

The most common findings on chest radiography, ECG, and laboratory testing are summarized in Table 12.3. Etiologic diagnosis may be suggested by viral cultures and titers, swabs of rectal and nasal mucosa, and acute and convalescent antibody titers. If EMB is performed, samples should be sent for viral and bacterial culture, as well as for PCR analysis.

12.5.2 Transthoracic and Transesophageal Echocardiography (TTE-TEE)

TTE-TEE is useful in myocarditis for many reasons: it is a noninvasive test useful to support clinical suspicion, and it provides assessment of LV performance,

functional and anatomical abnormalities of cardiac chambers, valvular apparatus, and pericardial involvement (i.e., in myopericarditis) and detection of intracavitory thrombi. Last, position of the cannulas, assessment of LV decompression, weaning process, and detection of specific ECMO-related complications could be easily and consistently followed by TTE-TEE. The exam usually reveals several degrees and extent of hypokinesis, associated with LV or biventricular systolic dysfunction, not necessarily associated with chamber dilatation. The most interesting aspect of TTE-TEE is the possibility of discriminating between fulminant and acute myocarditis: the first presents with a near-normal LV size and septal thickening, whereas the latter presents with increased diastolic dimensions and normal septal thickness. Both the clinical presentations were associated with a decrease in FS [30]. This knowledge is particularly useful in anticipating the need of ventricular support directly at presentation, and it allows to modify referral to ECMO centers and diagnostic and therapeutic pathways accordingly, as well as offering prognostic value.

12.5.3 Cardiac Magnetic Resonance (MRI)

Several reports showed that inflammation is reflected by signal changes in contrast-enhanced magnetic resonance imaging (MRI), due to the characteristics of gadolinium penetrating into extracellular fluid, but not into living cells: in acute inflammation, lymphocytic infiltrate, cell damage, and interstitial edema lead to accumulation of contrast in inflammatory lesions.

Contrast-enhanced MRI is therefore useful to document the location and extent of inflammation.

Different studies report that within the first 2 weeks, myocardial damage is mostly focal and became more diffuse within 4 weeks, with the extent of the lesion correlating with LV dysfunction [31, 32]. Moreover, the sensitivity of MRI in identifying areas of inflammation and infiltration may guide EMB, thus theoretically improving diagnostic yield, and different viral species seem to produce different patterns of involvement of myocardium, further restricting differential diagnosis.

12.5.4 Endomyocardial Biopsy

Endomyocardial biopsy is the “gold standard” for a definitive diagnosis of myocarditis, and based on the clinical scenario, guidelines strongly recommend to perform EMB in selected cases: a new-onset HF (less than 2 weeks) with hemodynamic compromise and normal-sized or dilated LV (fulminant myocarditis), a new-onset HF (2 weeks to 3 months) with dilated LV and new ventricular arrhythmias, II- or III-degree AV block, and refractory to standard treatment (GCM). Cardiac tissue samples may be obtained by standard EMB, which will be briefly illustrated, and by open surgical approach. At the present time, high-quality biotomes allow multiple sampling, commonly by transjugular approach (longer biotomes for transfemoral approach), usually guided by echocardiography (less commonly) or fluoroscopy,

with sampling mostly in the RV. It is reported that biventricular sampling may increase the diagnostic yield in myocarditis, compared to uni-ventricular biopsy, with comparable complication rate. Although hypothetically contrast-enhanced MRI could guide in choosing the ideal site to perform EMB, this was not confirmed. Complications of EMB are derived from case reports and include immediate (heart structure and great vessel damage, major arrhythmias, tamponade, pneumothorax, etc.) and delayed complications (bleeding, tricuspid valve damage, tamponade). Their relative incidence is unknown. Histologic examination reveals several patterns of infiltration (histiocytic and mononuclear), varying in severity and associating with structural abnormalities of myocardium. Despite being the actual gold standard, Dallas criteria interpretation of EMB has a low diagnostic yield. This depends on focal and transient nature of the disease, sampling error (either site choice or number of samples), possible disagreement in interpretation of histology even by expert pathologists, and most importantly issues concerning immunohistochemistry and PCR analysis, which were not routinely performed in earlier publications (hence the lower sensitivity) and the fact that some pathogens do not cause intense inflammatory reactions, therefore limiting histologic abnormalities of the cardiac tissue.

12.6 ECMO in Myocarditis

12.6.1 Indications

As previously discussed, myocarditis affects a group of patients with extremely severe cardiovascular failure, who paradoxically have a good prognosis and a high likelihood of return to normal cardiac function. This per se explains why this group could benefit from ECMO, mostly until recovery, a minority to an intermediate- and long-term cardiac support or to heart transplantation. Indications to ECMO could be summarized as cardiogenic shock and life-threatening arrhythmias, including SCD. Some patients will candidate for ECMO, during or after cardiac arrest; therefore, assessing the quality of resuscitation is mandatory before proceeding to mechanical support.

12.6.2 Diagnosis and ECMO

The diagnostic process needs to be adapted accordingly: noninvasive tests pose no particular dilemma and therefore should be immediately performed as soon as the suspicion arises. We underline once more the value of TTE-TEE in myocarditis, especially to discriminate fulminant myocarditis [30], to attempt predicting its rapid evolution, and to anticipate the need for ECMO. More invasive or unpractical tests need to be discussed further. First, it is well established that patients with myocarditis should be transferred to a specialized facility where EMB is available. Given the unpredictable nature of this disease and the extremely rapid evolution to LV

mechanical failure, we would suggest to transfer the patients to facilities where ECMO is available, to offer them adequate cardiovascular support, while still conducting the diagnostic process. Moreover, transjugular EMB is an invasive procedure, contraindicated if the patient is receiving anticoagulation for ECMO. To our knowledge, it is not reported in literature, nor it is the experience of either our center or of centers we mostly collaborated with, to perform EMB while the patient is on peripherally inserted ECMO, because anticoagulation and the impossibility of adequate hemostasis make the procedure unsafe. It is reported in literature that EMB was performed in myocarditis patients, shortly after they were weaned from ECMO still reaching an acceptable diagnostic yield. This would exclude patients with non-fulminant myocarditis, who would not be weaned from ECMO: most of these patients, anyways, will have indications to intermediate- or long-term VAD, which is usually performed with a central access through median sternotomy. A surgically performed biopsy, by expert hands and with immediate hemostasis, seems advisable for this category. Finally, patients with myocarditis will require diagnostic tests in remote facilities: we recommend an ECMO standby for high-risk procedures and for patients with high likelihood of rapid deterioration.

12.6.3 Which Support?

Literature accounts for numerous case reports or case series but a relatively small amount of large cohort studies, some of which were performed in children or young adults; therefore, some of the data reported here are extrapolated from pediatric population.

Both peripherally and centrally inserted ECMO are equally feasible in this group of patients, with slight advantage for percutaneous peripheral ECMO, for practical reasons. Most frequent percutaneous sites are jugular and femoral veins and femoral artery, although carotid artery is sometimes preferred, especially in children. Transthoracic approach usually requires right atrium and aortic cannulation. In some cases, the use of a secondary cannulation site is reported to optimize ECMO performance. Depending on the characteristics of the patients and occurrence of concomitant respiratory failure, circuit choice may be varied from standard extracorporeal centrifugal pump with an oxygenator to a paracorporeal non-pulsatile VAD without an oxygenator, to offer the advantages of lower heparin requirements. It is important to underline that some pathogens of myocarditis could affect the patient primarily or exclusively with respiratory failure: it is important to modify the approach to ECMO considering that purely respiratory patients (discussed elsewhere in the book) could evolve to cardiovascular collapse, therefore needing a switch from venovenous to venoarterial ECMO or to a combination of the two, or that isolated myocarditis may evolve to respiratory failure, therefore contraindicating the use of VAD for isolated cardiac failure. One of the largest published studies is a retrospective ELSO registry review, enrolling 260 ECMO runs in 255 (<18 years of age) patients, with the intent of defining survival outcomes, trends in ECMO use, and its complications [33]. Overall survival was 61 %, in line with adult population reported elsewhere [34],

with 12 % patients' deaths after weaning from ECMO and the remaining for ECMO withdrawal due to irreversible organ failure. Six of the seven transplanted patients survived to hospital discharge. Pre-cannulation variables correlating with poor outcomes are metabolic acidosis, more severe hypotension, pre-ECMO cardiac arrest, and enterovirus infection [33]. No major ECMO technical difference was reported between survivors and nonsurvivors, although ECMO for isolated cardiac failure carried better prognosis. Complications during ECMO are commonly reported in the majority of published literature, including major cardiac arrhythmias, renal failure requiring dialysis, neurologic complications (seizures, infarction, hemorrhage, and brain death, which in Rajagopal et al.'s study [33] interestingly were not higher in patients cannulated during CPR), metabolic acidosis, pulmonary hemorrhage (more prominent in pediatric population and mandating LA decompression with venting), DIC, higher cardiac enzymes [35], and hyperglycemia that are almost invariably associated with worse outcomes. Careful attention should be made to maintain good end-organ perfusion during ECMO: prevention and relief of abdominal compartment syndrome, avoidance or prompt reperfusion of ischemic limb, and prevention of organ and especially renal failure improved outcomes in many published papers [36]. Interesting to report, nearly 50 % of patients needing ECMO for refractory cardiac arrest survived [33]. The use of IABP is associated with a better outcome in several adult reports [35, 37].

Cannulation occurs early, usually in the first 24 h from presentation, whereas total ECMO duration depends on underlying disease, being shorter for fulminant lymphocytic myocarditis (<2 weeks), and reducing the need for early listing for heart transplantation or escalation to VAD. This usually occurs in patients who do not meet weaning criteria from ECMO after such period of time, mostly as a bridge to subsequent transplantation. A variety of LV decompression techniques are also described for left heart distention or lung edema [35]: LA or LV drain and ASD creation. In pediatric population, ventriculotomy for VAD implantation or venting is perceived as potentially detrimental for development of future arrhythmias or ventricular dysfunction [33]. A thorough discussion of indications, implantation, management, and weaning from VAD is beyond the scope of this chapter, and we refer the reader to the specific section in the book.

12.7 Prognosis and ECMO

Prognosis for fulminant myocarditis is paradoxically good: survival rates are reported up to 75 % with mechanical support and favorable long-term outcome at 6 months with complete recovery of LV function. GCM and eosinophilic myocarditis have overall poor prognosis, with a relapse of disease when specific immunosuppressive treatment is discontinued and histologic recurrence post transplantation. Finally, we report an interesting paper on outcomes and psychophysiological assessment of 41 patients with fulminant myocarditis rescued by mechanical support (including 6 BiVAD and 35 ECMO). Compared to sex- and age-matched controls, myocarditis patients show satisfactory mental health and vitality but persistent physical- and

psychosocial-related difficulties, with about a third of patients showing symptoms such as PTSD, anxiety, and depression, therefore underlining the need for optimizing strategies aimed at reducing emotional distress and its long-term sequelae [34].

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13.1 Introduction

A few years ago, while still at medical school, I was sitting at a wedding dinner, when a consultant cardiac surgeon challenged the table with this joke: “What’s the difference between God and a cardiac surgeon? Well, God doesn’t think he is a cardiac surgeon!” Without digressing into a metaphysical discussion, it is evident that the impressive progresses of the last few decades, in both fields of science and technology, have dramatically changed the management of cardiac conditions previously deemed “too high risk”.

The use of extracorporeal membrane oxygenation (ECMO) as cardiopulmonary support has paved the way for new operative indications for those patients who were previously relegated to conservative medical management. This may have been because of poor left ventricular function, cardiogenic shock with complex multi-vessel disease, or multiple other co-morbidities. Recent applications have shown ECMO to be potentially effective as a temporising measure or bridge to therapeutic intervention in the setting of myocardial dysfunction and cardiogenic shock.

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The combination of a compact pump-oxygenator design, with smaller, percutaneous, flexible cannulae, makes the modern veno-arterial VA ECMO an ideal miniaturised cardiopulmonary bypass; it is easy to set up and to accommodate at the patient bedside. The 2009 H1N1 epidemic [1] exposed our unit to a more extensive use of veno-veno VV ECMO. The consequent increase in expertise, and level of familiarity with extracorporeal life support, extended its use to many others scenarios. Some of these include various high-risk catheter-based procedures, like percutaneous coronary interventions (PCI) and transcatheter aortic valve implantation (TAVI) [2–4], post-infarct ventricular septal defect (PI-VSD) repair, surgery on the thoracoabdominal aorta, international retrievals for respiratory and cardiac failure [5], and bridge therapy before urgent pulmonary thromboembolectomy (PTE) [6].

As there is a paucity of prospective, randomised controlled trials in this area, the evidence behind the use of VA ECMO during high-risk procedures has had to rely on retrospective series or case reports. In this chapter, we will review the main indications for the use of VA ECMO for emergent support or backup during high-risk procedures.

13.2 ECMO Support in High-Risk Coronary Angioplasty

13.2.1 Elective PCI in High-Risk Patients and Left Main Procedures

Patients with unstable angina and ischaemic cardiomyopathy with poor left ventricular function represent a subgroup at high risk for either percutaneous or surgical revascularisation. In this context, a transient coronary occlusion during angioplasty can precipitate profound instability, irreversible arrhythmia, or fatal loss of cardiac output.

ECMO-assisted PCI was initially introduced more than 20 years ago to provide haemodynamic backup in the event of acute coronary occlusion post angioplasty. In 1988, Vogel reported the first experience from the University of Maryland with supported PCI and valvuloplasty in high-risk patients (nine and six, respectively) [7]; patients were defined as high risk if they presented with severe left ventricular impairment or large amounts of myocardium perfused by the index vessel. In this early experience, all patients were weaned off bypass within 90 min (pump flow between 3 and 5 L/min) and the initial outcome was encouraging, with only one reported death in each group (acute mesenteric ischaemia 8 h after PCI and sudden ventricular fibrillation 12 h after valvuloplasty).

The following year, Taub et al. reported their experience with patients for whom ECMO-supported PCI was necessary because of low left ventricular ejection fraction (mean LVEF 31.5 %, $n=7$) [8]. The mechanical support permitted safe, longer balloon inflation time, yielding satisfactory angiographic results. However, this was at the expense of high complication rates in other areas, such as groin haematoma (requiring transfusion), deep vein thrombosis, and iliac artery occlusion, as well as a death from retroperitoneal haemorrhage. Similar results were described by the

University of California on patients with unstable angina and ischaemic cardiomyopathy (mean LVEF 24 %, $n=5$) who successfully underwent ECMO-assisted PCI [9]; the main drawback was again the high rate of access site complications. This is also probably a reflection of old cannulation technology.

More recently, Magovern reported the Allegheny experience with 27 high-risk patients who were revascularised with PCI under ECMO support [10]; technical success was achieved in 26 patients (96 %), including 12 requiring left main angioplasty. Most patients (85 %) survived to discharge, with sudden cardiac arrest and heart failure as the main causes of the death in the remainder.

Left main coronary artery (LMCA) disease is usually an indication for surgical revascularisation. However, patients at prohibitive risk for coronary artery bypass grafts (CABG) can be directed to the angiography suite, accepting that unprotected LMCA stenting in the high-risk population carries a mortality of 9 % at 30 days and 11 % at 1 year [11]. Significant risks associated with worse outcomes in the treatment of unprotected LMCA include a severely reduced LVEF (<35 %), a synchronous right coronary artery (RCA) occlusion, the use of angioplasty without stents, and the presence of significant co-morbid conditions (older age and renal and respiratory failure). ECMO-supported LMCA stenting has been successfully reported for the first time in 1996 by Irons et al. [12]; they described the case of a 70-year-old woman with intractable unstable angina despite heparin, nitrates, and an intra-aortic balloon pump (IABP). She was deemed to have unacceptable surgical risk due to end-stage COPD ($FEV_1 <0.46$). She tolerated ECMO-supported LMCA stenting with multiple high-pressure balloon inflations and only a transient sinus bradycardia, but no ST changes or haemodynamic instability.

Likewise, other successful cases have been reported [13]: our first patient was an 81-year-old gentleman, who presented post STEMI with a 90 % LMCA stenosis and an estimated mortality risk by logistic EuroSCORE of 47 % [2]. The procedure was performed under general anaesthesia, and ECMO cannulation was established after femoral cut-down and a single bolus of 10,000 units of intravenous heparin. ECMO flow was maintained at 2.5 L/min for the duration of the case, and weaned off after LMCA and RCA stenting. Note, we have since moved on to percutaneous cannulation with pre-close technique [4].

13.2.2 Emergent PCI Post Myocardial Infarction and Cardiogenic Shock

Patients with myocardial infarction (MI) who have out-of-hospital cardiac arrest and cardiogenic shock have a high mortality rate (5–10 % of all STEMIs) [14, 15]. The SHOCK trial has since reported improved survival of up to 6 years with early revascularisation compared to initial medical stabilisation and delayed revascularisation in this subset of patients [16]. The use of peri-procedural circulatory support has become increasingly common with the availability of percutaneous left ventricular support devices such as the Impella recover LP2.5 (Abiomed Europe GmbH, Aachen, Germany), TandemHeart (Cardiac Assist inc., Pittsburgh, PA) [17], or the

use of IABPs. However, such devices support only the left ventricle, cannot take over the patient's gas exchange function, have high disposable costs, and lately the use of IABP in this setting has been strongly questioned [18]. If systemic hypoxia cannot be treated rapidly and effectively, the oxygen supply to the heart, brain, and tissues will remain poor; restoration of spontaneous circulation will then be very unlikely.

VA ECMO provides a less expensive full cardiopulmonary support in patients who suffer an acute and profound but potentially treatable cardiac insult, complicated by cardiogenic shock and recurrent cardiac arrest despite inotropes and IABP [19, 20]. Patients with profound cardiogenic shock will often present with a cardiac index below 1.5 L/min/m² and consequent acidosis secondary to hypoperfusion leading to multi-organ failure. Prompt initiation of ECMO support with a flow rate of 2.5–5 L/min, depending on the patient's afterload and intravascular volume, will quickly stabilise the haemodynamic status, providing adequate cardiac output and peripheral perfusion [21]; once rescued from the acute insult, the patient can "rest on ECMO" until complete revascularisation with PCI or coronary bypass is achieved [22].

In the case of intra-procedural cardiac arrest, rapid mechanical chest compression is initially necessary to prevent no or low blood flow episodes [23]. However, external cardiac compression is often not compatible with successful PCI, leading to loss of wire access in the target vessel, unsuccessful revascularisation and prolonged procedures, or complete breakdown. Mechanical chest compression devices can be supportive but are often responsible of severe thoracic and intra-abdominal damage [24].

Lee et al. reported two cases of VA ECMO-assisted PCI in patients suffering cardiac arrest and cardiogenic shock post STEMI [25]: one patient was successfully bridged to transplant after ECMO-supported PCI, while the other one survived the initial procedure but succumbed later to a severe anoxic brain injury. In this scenario, timing is essential: "door-to-balloon" time should be within maximum 45–60 min. If circulatory support is necessary, ECMO should be ideally established within 10–15 min. This requires all of (1) impeccable coordination between cardiac surgeons, cardiologists, perfusionists, and anaesthetists; (2) familiarity with percutaneous cannulation; and (3) prompt availability of cannulae in different sizes and lengths.

Despite ECMO support, the outcome in this setting remains dismal. In a retrospective review of 36 patients with post-MI cardiogenic shock necessitating extracorporeal mechanical support, PCI was attempted in 11 patients and was successful in only seven cases. Four patients were weaned from ECMO within 48 h, but none survived to hospital discharge [13]. Arlt et al. reported 50 % in-hospital mortality in a group of 14 patients who developed circulatory arrest in the cath lab during PCI or TAVI and required emergent extracorporeal life support [21]. In the PCI group (nine post-acute MI and one pre-transplant diagnostic cath), only four patients survived to hospital discharge. Finally, the Cleveland Clinic retrospectively analysed 138 patients who suffered post-acute MI cardiogenic shock [26]; patients who underwent revascularisation and circulatory support including ECMO as a bridge to cardiac transplantation experienced a significant 5-year survival benefit.

13.3 High-Risk TAVI and ECMO Support

The introduction of TAVI has revolutionised the management of aortic valve disease in the elderly and high-risk populations. In our recently reported experience, among the key points necessary to obtain good results, we identified the central role of the “heart team”. At the Royal Prince Alfred Hospital (The University of Sydney), TAVIs are performed as a joint approach between cardiologists and cardiac surgeons, in close collaboration with anaesthetists and perfusionists, to facilitate appropriate bailout options in the event of complications [3]. All patients are offered only temporary ECMO support; long-term extracorporeal assistance in the intensive care unit (ICU) is futile and inappropriate in this elderly and frail population.

We prefer ECMO to a full cardiopulmonary bypass (CPB) circuit for reasons of space, reduced circuit prime, reduced activated clotting time (ACT) requirement, and ease of use. VA ECMO has been used liberally in the elective situation, in particular for patients with poor left or right ventricular function and in patients with incompletely treated coronary artery disease. It has also been used emergently for acute right heart failure, cardiac decompression to manage left ventricular apex haemorrhage, and various rescue procedures; some of these include valve-in-valve sealing of aortic root rupture, managing valve embolisation and thoracotomy for tamponade decompression. All patients have reperfusion and rest on ECMO or are transferred to an operating theatre for rescue surgery if that is deemed appropriate before undertaking TAVI.

In 2010, Webb reported the outcome of the Canadian experience with 345 TAVI patients at very high or prohibitive surgical risk [27]. The 30-day mortality was 10.4 %, while a further 14 patients (4.1 %) needed haemodynamic support with IABPs (0.9 %), or extracorporeal circulation (2.9 %), or both (0.3 %); this was due to severe maintained hypotension or haemodynamic collapse secondary to acute severe left ventricular dysfunction (2.9 %), ventricular apical bleeding (0.9 %), or cardiac perforation (0.3 %). The need for intra-procedural haemodynamic support was significantly associated with higher 30-day and late mortality.

Recently, a group from the University of Regensburg in Germany updated their experience with emergency and prophylactic use of ECMO during TAVI [28]. Initially, they limited the use of VA ECMO to bailouts for intraoperative complications in 8 out of 131 cases (including ventricular perforation, cardiogenic shock, and ventricular tachycardia). VA ECMO was then used prophylactically in nine patients who were deemed very high risk. The median logistic EuroSCORE in this subgroup was considerably higher compared to the remaining TAVI population (30 % vs 15 %, $p=0.0003$), while in the emergency ECMO subgroup it was comparable. The use of prophylactic VA ECMO had a significant positive impact on procedural success ($p=0.03$) and 30-day mortality ($p=0.02$) compared to emergency extracorporeal support.

13.4 ECMO Support for Post-infarct VSD

Post-infarct VSD (PI-VSD) is a well recognised, and now rare (0.3 %), complication of MI, with very significant morbidity and mortality [29]. Despite the high risks associated with surgery [30] or percutaneous interventions [31], medical

management on its own has an almost 100 % mortality [32]. The timing remains controversial: a careful balance between the need for early VSD closure to avoid haemodynamic collapse and delayed closure to allow recently infarcted myocardial tissue to organise to enable closure needs to be respected. It is not surprising that those patients with cardiogenic shock and multi-organ failure have the highest mortality [33]; in this subset of patients, VA ECMO can restore perfusion, provide organ support, and allow repair in a more controlled clinical situation [34, 35].

Recently, we provided mechanical cardiopulmonary support in two very high-risk patients with PI-VSD and cardiogenic shock (logistic EuroSCORE 80 %). The first case involved a 60-year-old man who suffered cardiogenic shock 4 days after VSD-complicated MI, with severe left and right ventricular failure; VA ECMO (femoro-femoral) was used as a bridge to definitive surgical double-patch (Daggett) repair. Immediately after institution of ECMO, there was normalisation of metabolic parameters and significant wean from inotropes was possible. The second patient presented with cardiogenic shock secondary to PI-VSD who continued to deteriorate despite maximal medical therapy (IABP and inotropes), with impending multi-organ failure and metabolic acidosis; VA ECMO (femoro-axillary) was initiated to restore organ perfusion and delay VSD closure. After a week on mechanical support, his clinical condition stabilised dramatically, with resolution of renal and hepatic failure. He underwent successful VSD repair with a pericardial patch and bioprosthetic mitral valve replacement. Both patients required post-operative VA ECMO support, and they were eventually decannulated, surviving to hospital discharge.

Various case reports have suggested that extracorporeal support may be an option to allow haemodynamic stability, thus allowing a delayed closure approach. Initial reports utilised ventricular-assist devices (VAD) to bridge patients to definitive surgical repair [36]. VAD support requires a sternotomy and involves cannula placement in stunned and recently infarcted myocardial tissue in a patient with multi-organ failure [37]. VA ECMO is less invasive, does not require a sternotomy, and provides cardiorespiratory support, thus allowing a period of cardiac “rest” and restored organ perfusion prior to attempting surgical closure. The recent literature on VA ECMO support for cardiogenic shock does report the use of VA ECMO in cardiogenic shock secondary to PI-VSD. However, it is not clear if ECMO was initiated prior to operative intervention [38].

13.5 ECMO and Acute Pulmonary Embolism

Patients presenting with massive acute pulmonary embolism (PE) complicated by right ventricular (RV) failure and cardiogenic shock have a poor prognosis [39]. Urgent thrombolysis or embolectomy is mandatory; however, these therapeutic measures might not be initiated immediately due to haemodynamic instability or logistic reasons. Mechanical support in these circumstances is essential as a stabilising measure or bridge to further interventions [40]. The use of right VADs has been described, but carries the risk of even further elevation of pulmonary artery (PA) pressures to suprasystemic values [41]. VA ECMO is an optimal strategy in RV

failure cases resulting from pressure overload secondary to pulmonary obstruction. Misawa et al. [42] reported two cases in which percutaneous VA ECMO was used as an adjunct to thrombolytic therapy for progressive circulatory collapse secondary to massive acute PE. In both cases, restoration of haemodynamic stability was readily achieved once ECMO flow was initiated.

When cardiogenic shock secondary to acute RV failure increases the risks of immediate surgery, VA ECMO is a useful bridge option. In our case, a 56-year-old man presented with acute massive PE and paradoxical embolism, with obstruction of the infrarenal aorta and ensuing mesenteric ischaemia [6]. After emergency aorto-mesenteric embolectomy, peripheral VA ECMO was established and continued for 2 days as a bridge to successful PTE. A similar case was described by Deehring et al. [43]: a 17-year-old presented with acute PE and rapidly deteriorated with cardiogenic shock secondary to acute RV failure. Despite intubation and cardiopulmonary resuscitation, she remained unstable and required VA ECMO cannulation in the emergency department prior to transfer to a paediatric hospital where she underwent successful PTE.

Finally, some patients will persist in refractory cardiogenic shock despite operative management. Howes et al. recently presented the case of a 38-year-old man who experienced acute deep venous thrombosis (DVT) and PE following knee arthroscopy [44]; despite thrombolytic therapy with alteplase, the patient remained hypotensive, and peripheral VA ECMO was initiated and continued until restoration of RV function. Similarly, Belohlavek et al. reported a 51-year-old man who presented with recurrent PE 1 year after previous PTE [45]; surgery was not indicated due to severe RV dilatation and systolic dysfunction, so he underwent thrombolysis but within minutes, he experienced ventilatory and haemodynamic collapse secondary to further embolisation. Peripheral VA ECMO was immediately started at 2.5–3 L/min and continued until day 4 post successful redo PTE.

13.6 Cannulation and Complications

The most common arterial access sites for peripheral ECMO are the femoral and axillary arteries with surgical exposure, direct cannulation, and purse-string control of the arteriotomy; the use of a Dacron interposition conduit is preferred in case of diseased vessels. Percutaneous cannulation with vessel closure device (PerClose Proglide, Abbott Vascular, Redwood City, CA, USA) is also safe and effective in the right patients and experienced hands (Fig. 13.1) [4]. Axillary perfusion is preferred in patients with severe cardiopulmonary dysfunction requiring high-flow bypass [46]. The femoral vein is almost universally used as drainage site.

The main disadvantage of ECMO over full cardiopulmonary bypass is the lack of myocardial protection with cardioplegia and ventricular decompression. Moreover, in case of aortic regurgitation or bradyarrhythmia, peripheral retrograde flow can lead to ventricular overtension.

In case of heparin-induced thrombocytopenia, anticoagulation during ECMO can be safely achieved with the use of bivalirudin [47].

Fig. 13.1 Percutaneous femoral cannulation with Preclose technique using PerClose Proglide vascular closure device (Abbott Vascular, Redwood City, CA, USA)



Finally, a point has to be made on safe cannulation; many patients experienced severe and catastrophic complications from iliac rupture or uncontrolled groin bleeding. In elective situation they are avoidable with careful preoperative workup (arterial CT angiogram to avoid calcified and tortuous vessels). Careful haemostasis is crucial especially when ECMO support follows thrombolysis post STEMI or PE [44, 45].

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Peter Mair and Elfriede Ruttman

In general, emergency mechanical circulatory support for the treatment of prolonged, intractable cardiorespiratory arrest is assigned only a low-grade recommendation in current resuscitation guidelines [1]. However, for cardiorespiratory arrest associated with severe accidental hypothermia, emergency mechanical circulatory support and extracorporeal rewarming are widely recommended and considered the gold standard of treatment [1–3]. Increasingly, venoarterial ECMO systems are being used for extracorporeal support in hypothermic patients, as ECMO not only offers significant advantages as compared to standard cardiopulmonary bypass (CPB) technology but may also be associated with improved survival [4, 5].

14.1 Accidental Hypothermia and Hypothermic Cardiorespiratory Arrest

Accidental hypothermia is defined as an involuntary drop in body core temperature below 35 °C [1, 2]. Respiratory and cardiocirculatory functions are not significantly impaired as long as core temperature does not drop below 32 °C [2, 6]. When body core temperature falls below 32 °C to 30 °C, patients present with impaired consciousness, reduced respiratory rate, bradycardia, and hypotension [2]. With further cooling deep coma with fixed, dilated pupils develops together with very slow gasping respiration and reduced cardiac output, making detection of vital signs difficult [6]. Reduced cardiorespiratory function per se does not put the patient at risk for

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irreversible injury, but instead is a physiological response by the human body to the reduced oxygen demands during hypothermia [6]. If core temperature falls below 20 °C, respiratory arrest and asystole will eventually occur [6].

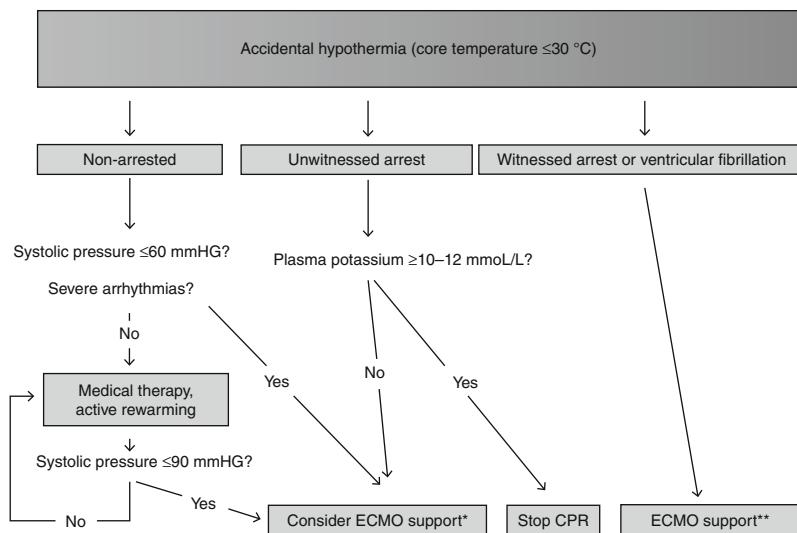
The heart of a patient with severe accidental hypothermia and a core temperature below 30 °C is not only bradycardic but also highly irritable and prone to arrhythmias [1, 2, 6]. At a core temperature below 30 °C, minimal alterations in the heart or minor movements of the patient can result in ventricular fibrillation, the so-called hypothermic sudden cardiac death phenomenon [1, 2, 6]. The fibrillating hypothermic heart in general does not respond to electrical or pharmacological therapy unless rewarmed [2, 3]. On the other hand, hypothermia offers significant protection from ischemic brain injury and enables full neurological recovery, even after resuscitation efforts lasting several hours [2, 3, 6]. Consequently, it is difficult to diagnose irreversible cardiorespiratory arrest during hypothermia. That being the case, death in a hypothermic patient should be defined as “failure to revive with rewarming,” and it is widely accepted that “nobody is dead unless warm and dead” [6].

Asystole in arrested hypothermic patients indicates very low body core temperature, prolonged cardiac arrest, or concomitant asphyxia, and ventricular fibrillation indicates cardiac arrest due to arrhythmias induced during rescue or initial treatment. Consequently, hypothermic cardiac arrest associated with ventricular fibrillation has a far better prognosis than does hypothermic cardiac arrest in an asystolic patient [2, 3].

14.2 Indications for ECMO in Patients with Severe Accidental Hypothermia

ECMO is associated with a significant risk for major complications. Most patients with severe accidental hypothermia and a core temperature below 32 °C can be successfully treated with noninvasive external rewarming or minimally invasive techniques of internal rewarming [2, 6]. Consequently, most clinicians do not use ECMO, even in a profoundly hypothermic patient, as long as the patient can be stabilized with medical therapy. ECMO support is usually restricted to patients with severe hemodynamic compromise or cardiorespiratory arrest [1–3] (Fig. 14.1). It has been suggested that also some non-arrested hypothermic patients (e.g., those with a history of asphyxia or near-drowning) may benefit from more aggressive use of ECMO support instead of medical therapy [5, 7].

ECMO is available in only a few specialized centers. Many cases of accidental hypothermia, however, occur in remote areas, and long transfer times are necessary to provide ECMO support. For this reason, alternative therapeutic approaches have been used that combine prolonged external chest compression and alternative rewarming techniques (e.g., hemofiltration, hemodialysis, peritoneal lavage, thoracic lavage) [2, 3, 6, 8]. A technique widely available, even in small hospitals, is closed chest thoracic lavage [3, 8]. Although alternatives may be successful in some cases, extracorporeal support is associated with higher survival rates [2]. Whether transfer to an ECMO center is the best approach must be decided on a case-by-case



*Use in selected arrested patients, may improve outcome in non-arrested patients, **Therapy of choice, use if available

Fig. 14.1 Indications for ECMO support in severe accidental hypothermia

basis, depending on transfer time, mode of transport available, experience of the attending physicians, and rewarming techniques available at the referring hospital.

Outcome of unwitnessed hypothermic cardiorespiratory arrest is poor as in many cases cardiac arrest precedes cooling, and there is insufficient protection from ischemic tissue injury. This is particularly true for hypothermic cardiorespiratory arrest associated with avalanche accidents and near-drowning [3, 9]. Insufficient protection from ischemia results in cell autolysis, which can be detected by high plasma potassium levels in some of these patients [2, 3]. Consequently, a plasma potassium level exceeding 10–12 mmol/L is considered the reason to withhold ECMO support in an asystolic hypothermic patient with unwitnessed cardiorespiratory arrest [2, 3] (Fig. 14.1). If plasma potassium is used to support the decision to terminate resuscitation, alternative reasons for severe hyperkalemia like extensive local freezing injuries must always be excluded [2, 3].

14.3 Advantages of ECMO as Compared to Standard CPB Technology in the Treatment of Severe Accidental Hypothermia

In many patients rewarmed primarily with CPB, ECMO later becomes necessary because of the inability to wean the patient from CPB due to intractable cardiorespiratory failure [10–13]. Furthermore, ECMO has significant advantages over standard CPB technology in emergency situations (Table 14.1). Thus, in an increasing number of hospitals, venoarterial ECMO has become the method of choice for

Table 14.1 Advantages of ECMO as compared to cardiopulmonary bypass in patients with severe accidental hypothermia

Provides more rapid extracorporeal support, thanks to its portable systems and short setup time
Cannulation and support are possible outside the OR
Lower levels of anticoagulation are needed
No systemic anticoagulation needed in case of major bleeding
Prolonged extracorporeal support is possible for hours and days
Easy patient transfer within hospital
Minimally invasive using percutaneous cannulation techniques
Negative pressure applied to venous cannulas enables higher extracorporeal flow rates

emergency extracorporeal support in hypothermic patients [4, 5, 13]. In a retrospective study of 59 hypothermic patients using multivariate logistic regression analysis, ECMO resuscitation was associated with improved survival as compared to standard CPB resuscitation [4]. The key factor responsible for improved survival was the routine use of prolonged cardiorespiratory support for 24–48 h in the ECMO group, thus preventing early mortality from respiratory insufficiency which is responsible for 64 % of fatalities after CPB resuscitation [4].

14.4 Clinical Experience with and Outcome Following ECMO in Severe Accidental Hypothermia

ECMO techniques (Table 14.2) have been used with success over the whole range of underlying pathologies associated with severe accidental hypothermia, including near-drowning [13], avalanche burial [4, 10], urban hypothermia [14], and multisystem trauma [15, 16]. Survival rates in published case series vary over a wide range and depend predominantly on the underlying pathology and preexisting co-morbidities [2, 3]. Urban hypothermia and hypothermia associated with avalanche accidents consistently produce poor survival rates [3, 6, 14], whereas hypothermia after prolonged exposure to cold in healthy individuals suffering from intoxication or wilderness accidents is associated with survival rates of 70–90 % in arrested patients [17]. Venoarterial and venovenous ECMO support have been used after CPB rewarming when patients cannot be weaned from extracorporeal support in the operating room because of intractable respiratory or cardiorespiratory failure [10–13, 18] (Table 14.2). Increasingly, however, venoarterial ECMO support with femorofemoral cannulation is used as the primary therapeutic intervention [4, 5]. Percutaneous femoral cannulation techniques have been used with high success rates and further reduce invasiveness [5]. ECMO is regularly implanted outside the operating theater, and transfer of the ECMO team to an outside hospital to implant an ECMO system in patients with hypothermic cardiorespiratory arrest has been reported [13, 19]. Even initiation of ECMO resuscitation at the scene may be a therapeutic option in the near future [20].

In most centers ECMO is used only in hypothermic patients with cardiorespiratory arrest. Based on their experience with 69 profoundly hypothermic patients,

Table 14.2 Clinical experience with ECMO in patients with severe accidental hypothermia

Venoarterial ECMO
Emergency mechanical circulatory support in arrested hypothermic patients
Immediate restoration of systemic blood flow before rewarming
Extracorporeal rewarming in profoundly hypothermic non-arrested patients
Rapid rewarming with cardiorespiratory support
Extracorporeal lung or heart/lung support after cardiopulmonary bypass rewarming
Inability to wean patient from bypass because of lung or heart/lung failure
Venovenous ECMO
Lung replacement therapy after extracorporeal rewarming
Upper body hypoxemia during prolonged femoral venoarterial ECMO
Lung failure after cardiopulmonary bypass rewarming
Extracorporeal rewarming in arrested hypothermic patients during ongoing CPR
Rapid rewarming in patients with no peripheral arterial access

Morita and coworkers suggested that ECMO may improve survival also in non-arrested patients [5].

Multiorgan failure, prolonged stay in the intensive care unit for weeks, and full neurological recovery after several months in a rehabilitation unit are regularly observed in hypothermic arrest victims after initial, successful resuscitation [10, 11, 21, 22]. Therefore, one should always be cautious not to terminate maximum therapy too early after ECMO resuscitation when the clinical course is complicated in a hypothermic patient.

14.5 Practical Issues of ECMO Support in Severe Accidental Hypothermia

Almost no scientifically valid data are available on how to manage a hypothermic patient on ECMO support. Consequently, perfusion protocols vary over a wide range among different institutions. As an example, the perfusion protocol used at Innsbruck University Hospital is shown in Table 14.3. Many institutions support patients with high flow rates in the range 2.5–3 L/m²/min also during hypothermia to compensate for a preexisting oxygen debt, although the optimal flow rate is in fact unknown. High rewarming rates are regularly used, at least until successful defibrillation of the heart. This enables early restoration of pulsatile flow and improved left ventricular unloading. On the other hand, it has been repeatedly stated that rapid rewarming may put the hypoxic, cold brain at risk for additional injury [2, 3]. Vasopressors to maintain mean arterial pressure above 50 mmHg, sodium

Table 14.3 ECMO perfusion protocol* for patients with accidental hypothermia*Cannulation*

Peripheral cannulation of femoral vessels using Seldinger technique

Percutaneous cannulation whenever possible

Use Seldinger technique after surgical cutdown and vessel exposure, if necessary

Always insert cannula for distal leg perfusion

Extracorporeal flow rates

High flow rates also during hypothermia

Anticoagulation

50–80 U/kg heparin before cannulation (no heparin in case of major bleeding)

Continuous heparin infusion to maintain ACT 150–250 s during ECMO support

Reduce (significant bleeding) or stop (life-threatening bleeding) heparin, if necessary

Temperature management

Start rewarming only after a period of hypothermic reperfusion to allow correction of abnormal blood values and insertion of additional lines

Rewarm no faster than 4–6 °C/h

Stop rewarming at 32 °C and maintain therapeutic hypothermia for at least 24 h

Defibrillate as soon as possible

Early restoration of pulsatile flow and improved left ventricular unloading

Weaning from ECMO

Do not wean immediately after rewarming

If possible, wean with moderate circulatory and ventilatory support after 12–24 h

Monitor blood gases and pulse oximetry on the right hand (upper body hypoxemia)

Transesophageal Echo Monitoring

Position of guidewire in arterial (descending aorta) and venous (right atrium) circulation during cannulation, reduced risk of major vessel injury during cannulation

Control and optimize venous cannula position during ECMO support

Monitor left ventricular unloading before defibrillation and during ECMO support

Monitor right atrial filling to optimize volume replacement during ECMO support

Near infrared spectroscopy monitoring (bilateral cerebral, both forelegs)

Monitor oxygenation and cerebral perfusion during CPR and extracorporeal rewarming

Detect “upper body hypoxemia” early during prolonged support

Monitor for ischemia in the cannulated leg during prolonged support

*Protocol used at Innsbruck University Hospital, Austria

bicarbonate to correct severe metabolic acidosis, and catecholamines to support left ventricular unloading and restore pulsatile flow are used, although their actual value has not been proven to date. Acid base management is normally done using an alpha stat regime. A systemic heparin dose lower than for standard CPB is almost always used, and the option of avoiding any systemic anticoagulation by using heparin-coated ECMO systems has been repeatedly mentioned [3, 4]. Nowadays, rewarming is normally discontinued at 32–34 °C in patients with a history of cardiorespiratory arrest and therapeutic hypothermia maintained for additional 12–24 h [23]. This approach is based on the extrapolation of data obtained during normothermic cardiorespiratory arrest. In some institutions prolonged ECMO support after initial resuscitation and rewarming is routine practice [4]. When prolonged femorofemoral ECMO support is used, “upper body hypoxemia” can occur in patients in whom recovery of myocardial function is more pronounced than is recovery of pulmonary

function (Table 14.3). This phenomenon is caused by poorly oxygenated blood that is ejected by the heart into the proximal parts of the aorta, whereas distal parts of the aorta receive well-oxygenated blood from the ECMO system. Therefore, oxygenation of the patient on prolonged femoral venoarterial ECMO must always be monitored on the right hand to detect this problem early (Table 14.3). If hypoxemia in the proximal aorta does not respond to alterations in mechanical ventilation, the patient must be switched to a venovenous ECMO system. Leg ischemia is a major complication of femorofemoral ECMO repeatedly reported [24]. Incidence of leg ischemia can be decisively reduced by inserting a separate cannula for leg perfusion. As kinking and dislocation of the cannula are possible in patients with distal leg perfusion, in particular during prolonged ECMO support, additional near-infrared spectroscopy monitoring of foreleg muscle perfusion is advisable. An organized, preemptive approach and standardized treatment protocols (Table 14.3) are used at several institutions [4, 5, 25] and are a good option for improving patient care.

14.6 Summary

Extracorporeal life support with ECMO is an increasingly popular alternative to cardiopulmonary bypass rewarming in hypothermic patients, as ECMO may improve survival and justify wider use of extracorporeal support, also in non-arrested patients.

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Drug intoxication (from abuse or from reactions not directly related to the dosage) may be associated with various clinical scenarios, sometimes primarily affecting the cardiovascular system and leading to such severe forms to provoke death. Indeed, if drug poisoning in general carries a low mortality rate (about 1 % in the adult), mortality appears much higher if cardiotoxic drugs are involved [1]. In a report of the American Association of Poison Control Centers, among 847,483 poisonings in adults over 19 years of age, cardiotoxic drugs were involved in 5.8 % but accounted for about 19 % of the total 1,261 poisoning fatalities [2]; it was also found that, though accounting for approximately 40 % of cardiovascular drug poisonings, calcium channel blockers and beta-blockers represented more than 65 % of deaths from cardiovascular medications [3]. Medical treatment for drug intoxication relies mostly on supportive measures or, in selected cases, on the use of antidotes. It is generally effective and well codified and appears to have reached high standards: further improvements might be unlikely. Nevertheless, the most severe forms of drug intoxication still carry a high mortality rate. The depression of cardiac function in drug intoxication is usually temporary and reversible: mechanical support to circulation can prevent death while waiting for the heart to recover.

15.1 Commonly Involved Drugs and Epidemiology

Most of the cardiotoxic drugs are membrane stabilizing agents (MSA). Already in the 1980s, Henry and Cassidy [1] showed that, for any pharmacological class of drugs, the mortality rate from poisoning is significantly increased if the involved drugs possess a MS effect in addition to their main pharmacological activity.

Membrane-stabilizing effect consists in the inhibition or total abolishing of action potentials from being propagated across the cell membranes. Substances with such

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effect interact with phospholipids in the cellular membranes, closing the sodium channels and therefore preventing the cell depolarization (action potential phase 0). For all the excitable cells (smooth or striated muscle cells, neurons, heart conduction system cells), this translates into (a) increased excitability threshold and (b) reduced conduction and automaticity. Cardiovascular, respiratory, and nervous system are mostly affected. Drugs with MS effect are Vaughan Williams class I antiarrhythmics, beta-blockers, antimalarial drugs, tricyclic antidepressants, phenothiazine, and cocaine. Other cardiotoxic drugs (without MS effect) are digoxin and calcium channel blockers (particularly verapamil). MSAs, digoxin, and calcium channel blockers are commonly prescribed drugs (apart from cocaine, which – though illegal – is a popular recreational drug), and this explains the prevalence of their abuse, which is almost always intentional (aiming to suicide or toxicomania related). Notably, when used for suicidal purposes, poisoning relies on the intake of multiple MSA.

15.2 Clinical Findings

Besides symptoms and signs that are typical for each class of substances, all the cardiotoxic drugs (MSA especially) lead to a common clinical scenario ruled by respiratory depression, metabolic disturbances, and – obviously – cardiovascular effects. The most typical presentation of severe cardiotoxicity consists in hypotension and/or severe cardiogenic shock. The electrophysiological alterations induced by the MSA lead to alterations on the electrocardiogram, typically enlarged QRS complexes and prolonged QT interval. In the most severe forms, disturbances of the atrioventricular conduction and ventricular arrhythmias (from tachycardia to fibrillation) can appear.

The delay in onset of life-threatening events depends on the toxicant and its galenic formulation, the ingested dose, the duration of QRS length on echocardiogram for the MSA, and the occurrence of mixed cardiotropic poisonings [4]. The delay is up to two hours after ingestion for class I antiarrhythmics [5] and of about 6 h for polycyclic antidepressants [6], chloroquine [7], and beta-blockers [8]. As reported by Baud et al. in an interesting review [4], in a non-negligible portion of cases, drug-induced cardiovascular shock does not result from a decreased cardiac contractility, but rather from a combination between relative hypovolemia and arterial vasodilation. This is well recognized for calcium channel blockers [2], less known for polycyclic antidepressants and chloroquine, and can be underestimated for labetalol poisoning. Therefore, in drug-induced cardiovascular shock with apparent refractoriness to conventional treatment, it is mandatory to perform a hemodynamic examination (using either right heart catheterization or echocardiography) to assess the mechanisms of shock before considering indication to mechanical support. In the same article by Baud, it was reported that, in 137 consecutive cases of severe MSA poisoning, survival rate for medically treated patients (catecholamines support in addition to specific treatments) was 72 %. Once again, this confirms that conventional therapy and pharmacological inotropic support are effective in most cases, while mechanical support must be restricted to the most severe forms only.

When treatment fails, death is usually related to ventricular arrhythmias, electro-mechanical dissociation, asystolia (usually preceded by other disturbances of the cardiac rhythm not responding to medical therapy), refractory cardiogenic shock, or cerebral death (the latter being common in patients who were found by rescuers in cardiocirculatory arrest).

15.3 Mechanical Circulatory Support for Drug Intoxication

Already in 2001, long before the resurrected interest in extracorporeal membrane oxygenation (ECMO) in many intensive care units around the world (fueled by the surprisingly good outcomes for its support in the 2009 A/H1N1 pandemic influenza), the toxicologic-oriented advanced cardiac life support (TOX-ACLS) guidelines stated that evidence supported the use of circulatory assist devices such as intra-aortic balloon pumps (IABPs) and emergency cardiopulmonary bypass (CPB) in the management of drug-induced cardiovascular shock refractory to maximal therapy [9].

Evidence comes from experimental studies and small clinical series. Five experimental studies with control group have been published [10–14]. In all of these studies, cardiogenic shock from MSA intoxication was induced. Drugs involved were lidocaine in 6 dogs [10], amitriptyline in 6 dogs [11] and 9 swines [12], desipramine in 6 dogs [13], and propranolol plus procainamide in 17 dogs [14]. The animals were assigned either to maximal supportive measures (i.e., correction of acid-base disturbances, fluid resuscitation, antiarrhythmics, inotropic support, or cardiopulmonary resuscitation, but no specific therapy for the intoxicant) or to mechanical support to circulation, by means of extracorporeal life support (ECLS) [10–13] or IABP [14]. In all of the studies, mechanically supported animals were all successfully weaned, while weaning rate in control groups ranged from 10 to 25 % only.

Clinical reports of mechanical support for cardiogenic shock in drug intoxication will be examined later in this chapter.

15.4 Options for Mechanical Circulatory Support in Drug Intoxication

Mechanical circulatory support in cardiogenic shock due to drug intoxication may rely on the use of IABP, CPB, or ECMO.

15.4.1 Aortic Counterpulsation

IABP is the most currently used form of mechanical support to circulation. The alternated inflation and deflation of the balloon, synchronized with the cardiac cycle, improve peak diastolic pressure and coronary blood flow while reducing end-systolic pressure, afterload, and myocardial oxygen consumption. It is the least

expensive form of mechanical circulatory support and it is easy and fast to deploy. It has been used alone to treat cardiotoxic poisonings induced by quinidine [15], propranolol [16], dextropropoxyphene [17], antihistamine [18], and a combination of verapamil and atenolol [19]. It has also been used in combination with ECLS in the case of organophosphate poisoning [20].

In this context, however, IABP shows some important limitations: in the first place, it requires some residual cardiac function to be effective and is totally ineffective when systolic arterial pressure is less than 40 mmHg or during a cardiac arrest. Another drawback is the impossibility of providing oxygenation, which might be needed in severe poisonings impairing the respiratory function.

15.4.2 Cardiopulmonary Bypass via Central Cannulation

CPB provides full circulatory support and oxygenation. It requires a full median sternotomy, so that a venous return cannula is inserted in the right atrium, while the arterial inflow cannula is inserted in the ascending aorta. Sporadic experiences are reported in literature [21, 22]: indeed, the strong limits to this technique are linked to its high invasiveness, the required setting of implantation (operatory room), and, therefore, the longer times required before ECLS can be provided. In case of cardiac arrest, it is not possible to deliver uninterrupted chest compressions before CPB is started. A prolonged assistance is inevitably associated with infective sequelae and higher rates of bleeding issues (a high anticoagulation regimen is required).

15.4.3 ECMO

Features and indications of ECMO support in the setting of refractory cardiogenic shock from drug intoxication do not differ from what has already been discussed in the previous chapters of this book. The possibilities of a complete cardiopulmonary support, a rapid deployment, and an implantation almost anywhere inside the hospital make ECMO the support of choice in the setting of refractory cardiogenic shock from drug intoxication. Peripheral cannulation through the femoral vessels allows continuation of chest compressions if the patient is in cardiac arrest. Requirements in terms of anticoagulation are minor; if compared with CPB, the infective risk is smaller and postoperative pain is avoided.

Nonetheless, the rate of complications is all but negligible, rising exponentially with the duration of support. Knowing this, and remembering the outcomes reported without ECLS [4], we once again underline that ECMO support should be reserved to very sick patients in whom the risk of death overcomes the risk of ECMO-related complications. On the other hand, as we will see later in this chapter, if we examine the outcomes reported in literature for ECMO support in cardiogenic shock, we will find that drug intoxication is one of the most favorable scenarios. Indeed, in this context the planned strategy for ECMO support is almost inevitably bridging to recovery.

The evidence on the subject relies mostly on isolated case reports and three case series. The first reported case series by Babatasi et al. dates 2001 [23]: six patients with cardiac arrest following acute severe self-administration of an overdose of beta-blockers, calcium antagonists, or antiarrhythmics were supported on femoro-femoral venoarterial ECMO. The first two patients died of multiorgan failure due to a delay in the installation of the assistance, while the remaining four patients survived without sequelae.

In 2009, Daubin and colleagues published the largest case series to date [24]: over a period of 10 years, out of 721 patients admitted for drug intoxication, 17 patients with refractory cardiogenic shock ($n=10$) or cardiac arrest ($n=7$) fulfilled the institution's criteria for ECMO implantation. In all of them, cannulation was achieved through the groin vessels and assistance was venoarterial. Thirteen patients survived and were discharged without significant cardiovascular or neurological sequelae. In 2012, Masson published the first retrospective cohort analysis comparing survival among critically ill poisoned patients treated with or without ECLS [25]. Sixty-two patients with cardiogenic shock ($n=42$) or cardiac arrest ($n=20$) following poisoning from drug intoxications were admitted in two centers over a time span of 10 years: 14 were treated with ECLS and the remaining 48 with conventional therapies. Global survival was 56 % (35 patients): 86 % in the ECLS group and 48 % in the non-ECLS group ($p=0.02$). Notably, none of the patients with persistent cardiac arrest survived with conventional therapy.

A recent review by De Lange et al. [26] extensively examined the literature on the subject: a total of 46 publications were found that dealt with ECMO support in drug poisoning. The authors concluded commenting that, in the absence of contraindications, the organ support provided by ECMO makes it especially useful in patients with severe poisoning, as the clinical impact of the intoxication is often temporary; therefore, ECMO can be used as a “bridge to recovery” and is a good salvage therapy for patients who are severely poisoned with acute respiratory distress syndrome (ARDS) or refractory circulatory shock.

The overall rate of complications (typically bleeding at the surgical entry site or intracranial hemorrhage) did not differ from reported complications for ECMO support in general.

The heart being the most severely affected organ in this subset of patients, it is important to remember that, though supporting the circulation, ECMO may have detrimental effects on the left ventricle. In fact, in a not negligible proportion of cases, the combination of severely reduced left ventricular function, blood return to the left atrium via the bronchial circulation, and increased afterload from the arterial cannula result in a dangerous rise in left atrial and ventricular pressures and pulmonary congestion [27]. The increase in wall stress due to left ventricular distention decreases myocardial perfusion and increases oxygen consumption leading to ischemia and reducing the likelihood of ventricular recovery [28]. In literature, a case of septal atriotomy to accomplish mechanical decompression of the left heart in patients with ECMO support for drug intoxication has already been described [24], but other methods are also available [29].

If the patient cannot be weaned from the ECMO support, the initial “bridge to recovery” strategy can turn into a “bridge to ventricular assist device (VAD)” or a “bridge to transplantation” strategy.

To date, no cases of switch from ECMO to VAD in drug poisoning have been reported. Nonetheless, it is technically feasible to alter the ECMO circuit in order to turn it into a left VAD for a potential midterm support by means of a left thoracotomy that allows the insertion of an outflow cannula in the apex of the left ventricle [29].

A case of ECMO as bridge to transplantation in a case of flecainide and betaxolol poisoning has been reported in 2010 [30].

15.5 Conclusions

In rare cases of drug-induced cardiogenic shock refractory to conventional therapies, the role of mechanical circulatory support is to sustain the cardiocirculatory system until the heart recovers. Intra-aortic balloon counterpulsation plays a role in less severe forms, in which it “helps” the failing heart. ECMO support is crucial when the cardiopulmonary function is severely depressed: it allows to gain time until recovery or until further options are available (heart transplantation, implantation of long-term devices). In the largest reported clinical series to date, weaning rate was 76 % with an average ECLS duration of 4.5 ± 2.4 days [24]. The relatively short duration of support for these patients translates into an acceptable rate of ECMO-related complications. In the light of the above reported results, drug poisoning appears to be one of the most favorable scenarios for ECMO support in cardiogenic shock.

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Newer Indications for ECMO: Pulmonary Embolism, Pulmonary Hypertension, Septic Shock and Trauma

16

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16.1 ECMO in Right Ventricular Failure

Massive pulmonary embolism (MPE) is a keystone in the history of ECMO, since the invention of the heart-lung machine was urged by the disappointing death of a patient suffering from this condition [1]. In 1931, Gibbon was assigned to monitor a lady with pulmonary embolism after a cholecystectomy; he had to call his chief when the situation was deteriorating at the point that a pulmonary embolectomy could be tried as a last chance. Gibbon [2] vividly described what happened:

During that long night, helplessly watching the patient struggle for life as her blood became darker and her veins more distended, the idea naturally occurred to me that if it were possible to remove continuously some of the blue blood from the patient's swollen veins, put oxygen into that blood and allow carbon dioxide to escape from it, and then to inject continuously the now-red blood back into the patient's arteries, we might have saved her life. We would have bypassed the obstructing embolus and performed part of the work of the patient's heart and lungs outside the body.

Then Gibbon and his wife started their experimental work on acute occlusive pulmonary hypertension and right ventricular failure [3, 4] and finally developed the heart-lung machine [2] reporting in 1937 the possibility to maintain circulation in cats with experimental occlusion of the pulmonary artery [5].

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Many years passed since then, but the indication for ECMO in supporting the failing right ventricle (RV) never subsided. The rationale of ECMO support in RV failure is to divert some blood from the right atrium to the arterial circulation, thus unloading the RV and relieving its dilatation, which in turn will lead to increased left ventricular output due to ventricular interdependence [6, 7]. ECMO relieves hypoxemia due to shunt in this setting and, through the required anticoagulation, provides also a therapeutic mean in thromboembolism.

In idiopathic pulmonary arterial hypertension, extracorporeal support is used to bridge patients to lung transplantation when medical therapy is exhausted or as a temporary aid in cases of increased cardiovascular requirement.

16.1.1 ECMO in Massive Pulmonary Embolism

Despite the great therapeutic armamentarium available for MPE, the reported mortality of patients presenting with RV failure and cardiogenic shock is still as high as 20–50 % [8].

Davies reported the first successful use of ECMO as a temporary support in MPE outside the operating room in 1995 [9]. It is noteworthy that the patient was kept conscious during the 6-day ECMO support. Plenty of case reports have been published since then on the successful use of extracorporeal support in MPE leading to cardiac arrest or cardiogenic shock [10–27]; some patients were treated only with ECMO, and others were successfully bridged to surgical or catheter thrombectomy. Case reports are biased by the high survival rate, since they report almost always on successful cases. Key points in the published case reports are the prompt institution of percutaneous ECMO, the achievement of haemodynamic stabilisation, the possibility to perform diagnostic exams during ECMO and the transport of the patient to a facility where surgical embolectomy could be feasible.

Maggio and co-workers [28] published one of the largest series, including 21 patients with MPE with profound shock and severe hypoxemia treated with V-A (19 patients) or VV ECMO (2 patients). The overall survival rate was 62 %. They pointed out the feasibility of the rapid institution of percutaneous ECMO support as a rescue manoeuvre also when the patients suffered cardiac arrest due to fulminant PE (8 cases). ECLS can be part of a therapeutic strategy comprising thrombolytics and other kinds of thrombectomies or can be curative with anticoagulation by itself. Daily follow-up with echocardiography would recognise the few patients requiring surgical embolectomy. Unfortunately, neurological complications leading to death were high in this patient population (4 patients, 50 % of the deaths).

Other case series [29–31] with good overall results have been published. Hashiba [30] reported 12 patients with fulminant PE in cardiac arrest at time of ECMO institution, 10 of them survived. The authors pointed out that both survival and neurological outcomes of cardiac arrest patients with MPE were better compared to the outcomes of 16 patients with post-acute myocardial infarction cardiac arrest (survival 83.3 % vs. 12.5 %, $p < 0.001$; good neurological outcome 58.3 % vs. 6.3 %, $p = 0.004$).

Recently, Sakuma [32] reported the Japanese experience with percutaneous ECMO as adjunctive support in MPE. 193 cases were collected from the literature; the overall survival rate was 73, 65 % in patients with cardiac arrest at the time of ECMO institution and as high as 86 % in those with cardiogenic shock.

In conclusion, ECMO support is of established benefit in patients with MPE-related cardiac failure, and it is recognised as a fundamental step in its interventional treatment algorithm [33, 34].

16.1.2 ECMO in Pulmonary Arterial Hypertension

The term pulmonary hypertension (PH) comprises different clinical entities as pointed out by the 2008 Dana Point classification [35]. The importance of an early diagnosis and the recognition of common pathophysiologic mechanisms underlying some diseases are pivotal steps to establish an optimal management [36–41]. Furthermore, algorithms have been developed for the assessment and accurate classification of PH and for treatment allocation. Despite improvement in overall management for these patients, mortality is still high; poor prognostic factors are a scleroderma-associated diagnosis and indices of RV failure.

RV failure can supervene in the setting of pulmonary arterial hypertension (PAH) also if there is a response to pulmonary vasodilators. Its pathophysiology is largely reviewed in the literature [7, 42–47]: RV adapts better to volume overload than pressure overload, chronic pressure overload will cause RV dilatation and increase in wall stress leading to hypertrophic remodelling, RV ischemia can ensue and cardiac output will decrease due to ventricular interdependence. Treatment of RV failure depends on underlying disease and its stage [7, 45–47] and the chronic or acute presentation. ECMO can play a role in some conditions leading to RV failure as a temporary support in “crisis” deteriorations or most commonly as a bridge to transplantation.

Veno-venous ECMO has been successfully used in cases of RV failure due to chronic pulmonary embolism hypertension after pulmonary endarterectomy to treat reperfusion syndrome or persistent pulmonary hypertension after surgery [48, 49]. In a recent survey on surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension, Mayer reported a 9.6 % incidence of pulmonary reperfusion oedema, and 16.7 % of the patients had persistent pulmonary hypertension. The need for ECMO in this population was 3.1 % [50].

In idiopathic PAH, ECMO has been used with different indications. Pereszlenyi [51] reported the use of ECMO intra- and postoperatively in patients undergoing bilateral lung transplantation: ECMO allowed the maintenance of protective ventilation and a controlled reperfusion of the allograft.

VA ECMO is the choice if the patient is haemodynamically unstable due to global heart failure [52–54], but different approaches have been advocated to unload the RV. In the case of a patent foramen ovale, VV ECMO can succeed by itself in this task [55]. In other cases, VV ECMO plus an atrial septostomy has been applied [56, 57], or a shunt between the pulmonary artery and the left atrium (PA-LA) interposed with a low-resistance pumpless system [54, 58]. The introduction of ECMO

as “bridge to transplantation” in idiopathic PAH patients has been reported to decrease the waiting list mortality and was not associated with a worse outcome after transplantation [59].

Another ECMO indication is to overcome a pulmonary hypertensive crisis in otherwise stable patients on pharmacological therapy [55, 60] or in cases of abrupt RV failure due to anaesthesia as described in a parturient PAH patient [61]. In the last case, ECMO has also been used as a pre-emptive measure [62] during elective termination of gestation.

In conclusion, temporary support of RV failure with ECMO during hypertensive pulmonary crisis or its long-term use as a “bridge” to lung transplantation is largely reported in the literature. ECMO support before transplantation is now feasible in awake, non-intubated patients with the possibility to perform physical therapy while waiting for organ assignment and is associated with a better prognosis [63–65].

16.2 ECMO in Septic Shock

Septic shock in adults is mainly hyperdynamic, characterised by vasoplegia and unresponsive to fluid loading, and the mechanisms underlying its pathogenesis are well described [66, 67]. Nevertheless, Dellinger [68] defined, more than 10 years ago, septic shock as a “melting pot” of shock aetiologies, between which also a cardiogenic component can be present. Pathophysiologic mechanisms [69–72] and echocardiography findings [73, 74] of septic cardiomyopathy are now well characterised.

16.2.1 ECMO in Paediatric Septic Shock

Children and neonates with septic shock, due to their limited cardiac reserve, present in the majority of cases with a “cold shock” characterised by profound vasoconstriction, and therefore, a cardiogenic component is almost always at play [75]. For this reason, the first applications of ECMO in septic shock have been in neonates and children. Already in 1995, the Extracorporeal Life Support Organization (ELSO) published the registry results on neonatal sepsis [76] and few years after in paediatric septic shock [77]. The conclusions were that ECMO support should not be withheld in these populations, despite a higher rate of intracranial haemorrhage compared with the non-septic patients. Experience in the use of ECMO in septic shock children increased, with overall good results [78–81], and ECMO support is indicated in the clinical guidelines for the treatment of neonatal and paediatric septic shock [82]. Controversies exist about the utility of ECMO in specific groups of septic shock children, like in meningococcal septicaemia [83, 84]. Indeed, other authors pointed out that the mortality increases with age despite ECMO [85].

16.2.2 ECMO in Adult Septic Shock

In the early years, septic shock and bacteremia were considered relative contraindications to ECMO. The concern was that the ECMO circuit, entrapping bacteria, could behave as a culture medium [86]. Septic coagulopathy and the related increased risk of bleeding was also a contraindication. For these reasons, there are scanty reports, till the recent years, about the use of ECMO in adult septic shock [87, 88]. During the last decade, with the improvement in ECMO technology and its safety, we observed expanding indications for ECMO use, and its absolute contraindications are continuously challenged [89]. Some case reports on ECMO use in adult septic shock related to Hantavirus [90], malaria [91], Staphylococcus aureus [92], Neisseria meningitidis [93], H1N1 influenza [94] and necrotising soft tissue infections [95] have been recently published.

Two series have been recently accepted for publication. Bréchot [96] reports on 14 patients with “cold” refractory septic shock with a very low left ventricular ejection fraction and elevated systemic resistance vascular index: the survival rate was 71 %. The other series is from a single centre in Taiwan [97]: 53 patients in septic shock were treated with ECMO in a 6-year period, 40 % of them were in cardiac arrest at time of ECMO institution and the overall survival to discharge was only 15 %. Age greater than 60 years was associated with the worst outcome. The large difference in the reported survival can be at least in part explained by the presence of a cardiac arrest group in the Taiwan series; the French cohort has, indeed, a septic cardiomyopathy characterised by profound left ventricular ejection fraction and very high systemic resistances, like a “Takotsubo-like cardiomyopathy”, that can explain the high survival observed.

16.2.3 Conundrums in ECMO for Septic Shock

In our opinion, it is essential to distinguish three groups of patients when dealing with the use of ECMO in septic shock:

- (a) Patients with cardiogenic shock and sepsis. Most of them can be treated with peripheral VA ECMO, being the cardiac component prevalent over the respiratory one.
- (b) Patients with ARDS and hyperdynamic septic shock. In this setting, VV ECMO is preferred, and a reduction in catecholamine’s requirements is commonly observed at its start. Furthermore, a worse outcome of septic shock patients treated with VA ECMO compared with matched patients on VV ECMO has been recently reported [98].
- (c) Patients with a depressed left ventricular function and concomitant severe ARDS. In these cases, the use of peripheral femoro-femoral VA ECMO can result in deoxygenated blood being ejected by the left ventricle, due to the pulmonary dysfunction, and perfusing the heart, brain and upper body. A central VA ECMO [96] or a V-V/V-A hybrid ECMO can be used to overcome this

problem; in the last case, the use of a bicaval double-lumen cannula can prevent the cannulation of a new jugular venous site to increase the oxygen saturation in the right atrium/ventricle [99]. Some authors described a better outcome in patients on veno-venoarterial ECMO when ARDS was associated with cardiac compromise [100, 101].

16.3 ECMO in Trauma

Major trauma is a leading cause of death, particularly among young patients, in three different ways: (1) immediate death on stage due to intractable injuries; (2) early death (hours to few days) related to severe haemorrhage, cardiovascular/pulmonary failure or severe brain injury; (3) late death (days to weeks) usually as a consequence of post-traumatic ARDS and/or multi-organ failure. ECMO may be an effective and lifesaving strategy in both early and late trauma-related deaths. Since major causes of early deaths are haemorrhagic shock, hypoxemia, hypothermia, metabolic acidosis and coagulopathy, by means of VA ECMO, we can restore adequate tissue perfusion and oxygenation, achieve quickly rewarming and infuse massive fluids or blood products. Conversely, in the treatment of post-traumatic ARDS, VV ECMO ensures protective ventilation of the traumatised lung, providing adequate oxygenation and avoiding consequent multi-organ failure. The association of ARDS and traumatic brain injury leads to higher mortality rate [102]; lung protective ventilation, permissive hypercapnia and increased intra-thoracic pressures used in ARDS may lead to worsening brain injury. VV ECMO could resolve this therapeutic “conflict” allowing adequate pulmonary support and lung rest and minimising secondary brain damage [103].

The indication for VV ECMO support in the early phase may be refractory hypoxemia and/or severe hypercapnic acidosis despite full conventional treatment. Conversely, VA ECMO support should be instituted in case of persisting shock, with signs of tissue hypoperfusion, despite fluid resuscitation, blood transfusion and vasopressor support or in case of post-traumatic cardiac arrest. Overall, in the absence of specific trauma guidelines, ECMO institution may be considered when clinicians are convinced that standard therapies have been exhausted in patients with potentially reversible injuries [104, 105]. Larsson and colleagues recently suggested that VA ECMO can play a possible role in the control of pulmonary bleeding since it reduces pulmonary perfusion; furthermore, it may be helpful during surgery since the jugular-femoral approach allows inferior vena cava clamping without compromising systemic organ perfusion [106].

Since the first successful use of ECMO in a trauma patient performed by Hill in 1972 [107], post-traumatic ARDS became a common indication for extracorporeal support. Furthermore, patients with post-traumatic ARDS were included in the major randomized trials on ECMO [108–111]. Early institution of ECMO (days on mechanical ventilation ≤ 5) has been associated with a better outcome [112] in this population. Finally, Bein and colleagues proposed the application of ECMO in hypercapnic patients with traumatic brain injury to minimise secondary brain damage [103].

16.3.1 Contraindications

Only few reports clearly listed contraindications to ECMO in trauma patients: (1) fatal cerebral lesions, (2) uncontrollable major bleeding (e.g. aortic rupture), (3) advanced age (>55–70 years), (4) witnessed prolonged hypoxemia (e.g. prolonged ineffectual resuscitation) and (5) potentially fatal pre-existing diseases [105, 113]. Prior to ECMO institution, a total-body CT scan is recommended, when feasible, to rule out the presence of absolute contraindications [104, 105].

Active bleeding, recent surgery and brain injury are recognised contraindications to anticoagulation and thus to ECMO, but recently several reports [104, 114–116] have been published on the successful use of ECMO in trauma patients after damage surgery, with severe brain injury or in bleeding shock.

16.3.2 Conundrums in ECMO Management in Trauma

16.3.2.1 Timing of ECMO Institution

Timing of ECMO institution depends on the clinical conditions and local resources; thus, emergency/urgent support is often established in emergency departments or in operating rooms during damage control surgery, while respiratory support in post-traumatic ARDS is mainly instituted in intensive care units. Emergency ECMO has also been instituted in austere settings like war zones to allow aeromedical evacuation of combat casualties to specialised centres [117–120].

16.3.2.2 Anticoagulation

Mostly in these patients, with high risk of bleeding, anticoagulation should be carefully managed with close ACT and/or aPTT monitoring. Some authors [104, 105, 115, 116] suggest heparin administration only after surgical bleeding control with a heparin-free ECMO running time of few hours or days. Others [114, 121, 122] apply standard anticoagulation protocol and prefer to stop or reduce heparin infusion only if bleeding occurs. Muellenbach reported one case of multiple thrombi in inferior vena cava after 3 days on heparin-free ECMO in a patient who however received recombinant factor VIIa (rFVIIa) for massive bleeding [115]. No other main thrombotic events were recorded, and bleeding complication rate was similar to “traditionally” ARDS patients undergoing ECMO.

Surgical procedures during ECMO are extremely frequent with low rate of bleeding complications [103–105, 112–116, 121–126]. Usually, if systemic anticoagulation is already established and surgery is scheduled, heparin should be interrupted few hours (4–6 h) before surgery.

The use of rFVIIa in massive bleeding in ECMO is controversial [127, 128]: despite the efficacy in bleeding control and, specifically in trauma patients, in reducing the risk of ARDS, some concerns remain on the risk of thrombotic events either in the circuit (circuit clotting or obstruction, oxygenator failure) or in the patients (stroke or pulmonary embolism). A higher rate of thrombotic events (33 % vs. 22 % in the adult population) was observed in the paediatric population, possibly due to differences in coagulation system and in ECMO circuit size [127].

In summary, when the risk of bleeding is very high (i.e., in trauma patients with intracranial haemorrhage, severe brain injury or bleeding shock), either low-dose heparin or temporary heparin-free ECMO could be used with some precautions: (1) high blood flow to reduce the risk of circuit clotting; (2) tight coagulation monitoring including D-dimer or fibrin degradation product (FDP), fibrinogen and platelet count; and (3) close membrane lung performance monitoring for early recognition of oxygenator failure/circuit thrombosis. Factor rVIIa may be considered in massive bleeding patients after correction of coagulation parameters, hypothermia, hypocalcemia and acidosis. After bleeding control, systemic anticoagulation should be started according to standard local protocol or with lower ACT/aPTT target if the risk of bleeding still remains high.

16.3.2.3 Traumatic Brain Injury

Traumatic brain injury is traditionally a relative contraindication to ECMO; however, several reports have been published on ECMO in patients with traumatic brain injury [103, 115, 116, 122, 123, 125, 129]. In all cases except one [122], intracranial pressure monitoring was established as soon as possible. Anticoagulation management was different among the reports: in some cases, heparin was started only after hours or days from ECMO institutions, with only one case of multiple thrombi [115]; in others, standard anticoagulation was performed, with a case of possible worsening in intracranial bleeding after ECMO institution [125].

Available data are not sufficient to make definitive recommendations; thus, each case should be carefully evaluated for benefits and risks of ECMO institution; in high-risk patients, ECMO should be run without anticoagulation and certainly with intracranial monitoring to promptly recognise and treat bleeding complications.

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17.1 Introduction

End-diastolic volume of the left ventricle (LV) is closely related to overall ventricular performance, as described by a landmark of cardiac physiology, such as Frank-Starling law. In the normal heart, myocardial fibers reach, at the end of diastole, a predetermined length, which is a balance between the filling pressure from the left atrium (LA) and the cardiac compliance. This is defined as preload of the LV. In the failing heart, this relationship alters, causing progressive dilatation of the LV and resulting in remodeling and worse systolic performance.

When LV contractility is profoundly impaired, inadequate right ventricular drainage and bronchial circulation can lead to left ventricular distension, increasing end-diastolic pressure and risk of pulmonary edema.

The purpose of ECMO support is, indeed, not only to achieve valid tissue perfusion indexes but also to provide ventricular unloading and wall tension control, providing rest for the failing heart. Mechanical circulation of blood through the cannulated vessels, per se, may not be sufficient to achieve this purpose, especially if the ventricles are enlarged and stimulated with high-dose inotropic drugs.

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Moreover, increased ventricular end-diastolic pressure results in increased wall stress and myocardial oxygen consumption, creating a vicious circle progressively worsening left heart failure. When mechanical support is indicated for cardiogenic shock of any etiology, it should be considered that inadequate right ventricular drainage and bronchial circulation could also contribute to LV distension. It is therefore of primary relevance to establish whether patients on mechanical support experience adequate LV decompression. This is particularly important in peripherally inserted ECMO (rather than orthograde flowing centrally inserted mechanical supports), in which it has been hypothesized that the combination of severe myocardial dysfunction and the adjunctive afterload, due to retrograde flow from the arterial cannula, could dangerously increase LV end-diastolic, LA, and pulmonary pressure (PA).

During VA ECMO, LV output must be carefully monitored to identify early changes of outflow and to guarantee effective opening of the aortic valve.

Even brief periods of overdistention will lead to worsening of myocardial damage. First-line interventions that can improve LV output include inotropes (e.g., dobutamine) to increase contractility and intra-aortic balloon counterpulsation (IABP) to reduce afterload and facilitate LV output.

Positive inotropic drugs act by different mechanisms to increase heart contractility and, as such, have been proposed for use in patients with cardiac failure to increase myocardial contractility and hence cardiac output. Indeed, in the short-term, acute phase of heart failure, inotropic drugs can be useful to increase cardiac output. On the other hand, prolonged stimulation with long-term inotropic therapy has been shown to increase mortality rates in patients with chronic heart failure.

Cardiac remodeling is manifested as a change in cardiac size, shape, and function. These modifications take place in response to either tissue injury or increase load, and it is thought to be an important factor in disease progression. The main clinical consequences of inadequate LV drainage could be summarized as follows.

First, mechanical supports are aimed mostly to ensure organ perfusion during profound cardiogenic shock but also adequate LV rest, allowing recovery of stunned myocardium and relieving shear stress from the necrotic area. Intuitively, if the support fails to provide adequate decompression, this results in direct dilatation of heart chambers, increasing oxygen consumption and ischemic damage but also adding mechanical damage to infarct area that could result in severe complications such as ventricular free wall rupture. Secondly, an enlarged, severely hypokinetic or akinetic cardiac chamber that doesn't provoke valve opening could cause blood stasis and intracardiac clot formation.

Hence, it is of paramount importance to ensure an adequate LV drainage, both to allow rest and recovery as well as to prevent severe life-threatening complications. Several techniques have been described to drain LV, including IABP, surgical or percutaneous venting, and axial impeller pumps. We will review the most relevant techniques to decompress the LV in ECMO patients.

17.2 Myocardial Dysfunction

Three major determinants of LV stroke volume and performance are the preload (venous return and end-diastolic volume), myocardial contractility (the force generated at any given end-diastolic volume), and the afterload (aortic impedance and wall stress). A thorough discussion of detailed physiology is beyond the scope of this chapter. During myocardial ischemia it is possible to recognize different pathophysiological entities, determined by the extent and duration in coronary flow alteration. The presence of malfunction is fairly common and clinically manifested as an alteration of the normal contractility of the heart wall.

Persistent, asymptomatic ischemia produces LV dysfunction that can mimic non-ischemic causes of heart failure and is defined as hibernating myocardium. Hibernation can be partially or completely restored to normal, either by improving blood flow or by reducing oxygen demand [1].

Transient ischemia can lead as well to a period of persistent dysfunction, even after the restoration of normal flow; this phenomenon is referred to as myocardial stunning.

Postischemic dysfunction or myocardial stunning appears to develop in various conditions involving the occurrence of transient ischemia, like unstable angina, acute myocardial infarction with early reperfusion, and cardiac surgery. Previous studies investigating myocardial perfusion and systolic function have noticed a close relation between reduction of blood flow and failing of contractile performance. Regional LV wall motion can persist for hours or days following reperfusion, despite the absence of irreversible damage and despite restoration of normal coronary flow. This tissue is still viable and the contractile abnormality is supposed to be reversible. The amount of flow which is normal at rest may not be adequate during exercise and there may be transmural variations in myocardial blood flow. Thus, it is possible that areas of dysfunction secondary to stunning and hypoperfusion may coexist within the same contractile area.

It has been observed in animals that a period of ischemia <3 h causes infarction of subendocardial portion of the interested region, whereas quantities of subendocardial tissue remained viable. The severity of stunning was greater in the inner layers of the left ventricular wall than in the outer layers, and this subendocardial tissue salvaged by reperfusion may require days or weeks to recover its contractile function.

Early reperfusion during acute myocardial infarction results in an admixture of thickened and stunned subendocardium. Factors that determine severity of cardiac dysfunction include size of ischemic region and loading condition of the heart. The process probably involves multiple factors, e.g., abnormal calcium homeostasis and oxidative stress among others [2–4]. Myocardial stunning is an important cause of post-resuscitation circulatory failure. Transitional global myocardial ischemia and profound depression of LV function are common after resuscitation maneuvers, and the resulting myocardial dysfunction has been documented in both animal and clinical studies. The compromise in systolic LV function is manifested by the decreased LV

ejection fraction, decreased fractional shortening, and decreased peak systolic LV pressure/end-systolic volume ratio. This kind of stunning can take place with no evidence of infarction, and both systolic contraction and diastolic relaxation remain impaired after myocardial blood flow is restored [5–10]. In some patients, areas of persistent ischemia can produce as well LV dysfunction, creating a condition of “hibernating” myocardium where coronary blood flow is chronically reduced. As blood flow is reduced, there is a corresponding reduction in contractile performance, and this coupling of low perfusion and diminished performance can take place with no ischemic symptoms or necrosis. In particular, this response of the heart coping with a reduced myocardial blood flow has been considered as an act of self-preservation. If blood flow remains low, the myocardium may be able to reduce its metabolic requirements still further, by undergoing a more chronic form of adaptation involving alterations in the morphology and protein content of the myocardium [11–13].

Whatever the cause, stunning and hibernation may cause significant cardiac failure. Structural remodeling would be necessary to restore contractility and adequate support is often necessary to achieve a satisfactory organ perfusion. As a result, chronically impaired but viable myocardium may take weeks to months to recover once flow is restored [14, 15].

17.3 Unloading in Chronic Heart Failure

Data collected in patients with chronic heart failure and left ventricular assist device (LVAD) show that myocardial unloading with an LVAD results in long-term recovery. The underlying process of myocardial recovery is still not completely understood, but previous clinical observations have shown that even cardiac patients with idiopathic dilated cardiomyopathy (ICD) subjected to strict measures of bed rest for long time showed improvement in symptoms [16]. Different theories suggest influences on the microvasculature, fibrosis, inflammation, and structural and cardiac remodeling. Furthermore, the combination of unloading and optimal coronary perfusion could facilitate a reduction in myocardial cytokines and a decrease in neurohumoral activity [17–19]. It has been observed that the heart can grow hypertrophic cardiomyocytes to reduce stress on the failing ventricular wall. Hetzer et al. showed that lasting recovery can be reached by ventricular unloading in a subset of patients with IDC, where LVAD unloading has been shown to induce regression of cardiomyocyte hypertrophy [20]. Klotz noted that LVAD support induced reverse structural remodeling of the heart, reducing LV size and myocyte dimensions and improving chamber stiffness [21]. Drakos collected hemodynamic data and LV tissue with digital microscopy coupled with ultrastructural and functional evaluation, speculating that pulsatile mechanical unloading of the failing heart increases microvascular density. The vascular changes were accompanied by increased fibrosis and reduced cardiomyocyte hypertrophy without any structural or metabolic evidence of outright degeneration and atrophy [22]. Even the beneficial effects of drug therapy with vasodilator therapy and angiotensin-converting enzyme inhibitor in afterload reduction on IDC hearts may be seen in the same context of LV unloading,

interrupting the links between decreasing in cardiac performance and increasing in systemic vascular resistance and LV filling pressure [23].

Despite previous observation, direct effect of mechanical unloading on myocardial endothelium and microvasculature is unknown and its effect on the degree of hypertrophy regression is controversial. Pathophysiological models have focalized attention on the role of excess load in driving a vicious circle of cardiac remodeling. Mechanical unloading would interrupt this cycle improving function of the failing heart. Recovery, if it occurs, is reached within a few weeks. Beyond this time, a process of gradual loss of ventricular function seems to take place [24–26].

17.4 Intra-aortic Balloon Counterpulsation

IABP is the most widely used form of mechanical hemodynamic support. AHA and European guidelines, respectively, give class IB and class IC recommendation to the use of an intra-aortic balloon in the treatment of cardiogenic shock [27, 28]. Nonetheless, the evidence provided is based mostly on registry data, whereas adequately powered randomized trials demonstrating the efficacy of IABP, beyond its physiological theoretical benefits, are still lacking.

Indication to clinical use of IABP includes [29, 30] mostly cardiogenic shock of any etiology, especially in complicating acute coronary syndrome, intractable arrhythmias, and adjunctive therapy in high-risk procedures. There is no sufficient literature, to our knowledge, to extrapolate definitive recommendations about the use of IABP in ECMO patients, and the controversies divide authors as supporters and nonsupporters, based on a single center's experience and clinical protocols. We'll briefly summarize pros and cons of IABP in ECMO and its physiological effects in terms of mechanical benefits and endothelial function, and we'll make an effort to provide some suggestions based on the presented literature.

Cyclic inflation and deflation of the balloon that provided significant interindividual variability (due to balloon size and position and physiological variables, such as heart rate and rhythm, compliance of the aorta, and systemic resistance) carry two major consequences: a displacement of blood through the proximal aorta during diastole and a reduction of afterload during systole through a vacuum effect due to rapid deflation of the balloon [31, 32]. Experimental and clinical studies suggest that afterload reduction and diastolic augmentation improve antegrade flow in coronary arteries, thus resulting in increased blood supply to territory perfused by a critically stenotic vessel [33], whereas hemodynamic effects on cardiac output are modest and do not impact on overall mortality.

The effect of IABP on coronary flow is still largely debatable: some studies have found little or no change in coronary blood flow, while others noted a significant augmentation [34–36].

Improved blood supply is higher where maximized autoregulation determines pressure-dependent perfusion and coronary vessel is fully dilated by ischemia. At lower perfusion pressures, IABP could increase blood supply even when coronary flow to the territory affected by the stenosis cannot be maintained. It is important to

mention that no improvement in coronary perfusion could be found distally to critical stenoses (>95 %) [37].

As far as mechanical effects, though, despite evidence, a theoretical benefit may be hypothesized, especially in acute mechanical abnormalities, such as mitral regurgitation (MR), ventricular septal defect (VSD), and non-pulsatile flow, resulting from ECMO. In fact, reported beneficial effects of IABP are a reduction of heart rate and mean pulmonary capillary wedge pressure, increase in cardiac output (especially when mechanical complications arise), and better perfusion of large territory of refractory ischemia. More interestingly, IABP reduces mean systemic impedance and systolic pressure, resulting in 14 % decline in calculated peak left ventricular wall stress [38]. This may represent the exact goal of afterload and wall stress reductions that is desirable to achieve in ECMO patients with otherwise sub-optimal LV protection.

Despite intuitive physiology, IABP does not, at present days, encounter global consensus, and no randomized trial is available to our knowledge to specifically address the issue of using IABP and ECMO. The most relevant literature supporting combined use of IABP and ECMO includes the following works.

Madershahian and colleagues showed that IABP in refractory cardiogenic shock, during non-pulsatile ECMO flow, may be beneficial in terms of coronary flow, graft patency in the early postoperative period, and compensation for lower ECMO pump flow to maintain equivalent bypass graft flow. However, the small number of patients does not allow conclusive evidence. Phillips et al. reported that a combination of peripherally inserted ECMO and IABP, in 16 cardiogenic shock patients, provided greater hemodynamic support and pulsatile flow during diastole, increasing coronary blood flow and allowing LV systolic decompression [39]. Lazar and associates [40] demonstrated a reduction of infarct size and reversal of hemodynamic deterioration, less tissue acidosis, higher wall motion scores, and the least amount of necrosis.

The last two groups of authors encounter our favor in supporting the use of IABP during ECMO: they suggest that application of these modalities can be readily instituted in emergency situations and produces optimal recovery of acutely ischemic myocardium, concluding that ECMO should always be used in conjunction with IABP support. They also proposed a staged protocol in mechanical support and weaning, by inserting first IABP and subsequently ECMO, and the opposite in weaning. Moreover, IABP may accelerate weaning from ECMO resulting in less heparinization and potential bleeding.

Finally, O'Neil et al. reported that pulsatile is superior to non-pulsatile perfusion in preserving the microcirculation and decreasing systemic inflammatory response during cardiopulmonary bypass (CPB), thus potentially improving outcomes in high-risk cardiac surgical procedures requiring prolonged CPB time [41]. This could be applied to ECMO patients, who are both in need of prolonged mechanical support, even if less pro-inflammatory than standard CPB, and are in the high-risk category.

Potential complications of IABP are well known to all physicians dealing with mechanical support for cardiogenic shock, and despite careful management, adverse

events are to some extent still unavoidable. Vascular complications (6–25 % of cases) are the major risk, including limb and visceral ischemia, vascular laceration, and major hemorrhage. It is mandatory to promptly address the issue of surgical repair as soon as the complication arises. Ultrasonography assessment of arterial vessels and guidance during placement, sheathless insertion, and adequate sizing of the balloon could help in minimizing complications.

If we do not support widespread use of IABP in all ECMO patients, we favor its placement for mechanical complications (MR, VSD, etc.) and for patients in which even a minimally pulsatile flow could not be achieved. IABP for weaning is discussed elsewhere.

17.5 Venting

Surgical Vent. Surgical left heart decompression is very common especially in valvular surgery and can be accomplished through insertion of an LA or LV vent. The cannula can easily be placed by the surgeon under direct vision, either in the LA or more commonly in the right superior pulmonary vein: this serves mostly to improve surgical field vision, by suctioning blood, and to prevent excessive ventricular distention. If longer-term support is anticipated, LV apical cannulation can also be a valuable alternative, and the need for sternal diastasis with central cannulation may influence the decision of whether or not to tunnel the vent.

If ECMO is initiated peripherally, decompression of the left ventricle is, to some extent, more difficult. In settings where the chest is not already open, decision for sternotomy/thoracotomy should carefully weigh the risk-benefit of a centrally inserted vent versus the risk of associated bleeding complications due to systemic anticoagulation. For this reason, a number of percutaneous techniques have been described: balloon and combined blade and balloon atrial septostomy under trans-thoracic (TTE) or transesophageal echocardiographic (TEE) guidance, transseptal sheath placement, transaortic cannula, percutaneous transjugular pulmonary artery venting, and impeller pumps.

17.6 Balloon and Combined Blade and Balloon Atrial Septostomy

Koenig et al. [42] described transvenous balloon atrial septostomy in four pediatric patients with cardiogenic shock from myocarditis. The technique is historically a modification of Rashkind procedure used to create atrial septal defects in children with transposition of great arteries.

Although theoretically beneficial, the procedure may pose some serious challenges: technically, if balloon septostomy is relatively easy to create in infants and toddlers due to soft atrial septum, this is far more challenging in older patients, in which septal thickening requires often the use of a blade technique, to achieve unrestricted left-to-right atrial flow. Moreover, blade septostomy, which is a valuable

alternative in difficult cases, often requires the use of fluoroscopic guidance and therefore exposes patients to potential adverse effects due to transfer and, especially in children, to radiation exposure. In fact, in Koenig's report, one procedure did not result in a hemodynamically significant atrial septal defect, and the older patient required blade septostomy to be performed under fluoroscopic guidance. Moreover, this procedure is technically feasible at the bedside only if a patent foramen ovale exists.

Later Johnston et al. [43] reported a 10 year-old patient, requiring decompression for pulmonary hemorrhage due to cardiogenic shock with severely dilated LV with an intracavitory thrombus. Drainage was achieved by creating an atrial septal defect, with transseptal puncture followed by progressive balloon dilatation, under transesophageal echocardiographic guidance. The advantages presented by Johnston et al. include the feasibility of this technique at the bedside, under TEE guidance, without risks and disadvantages due to fluoroscopy in catheterization laboratory and the fact that the procedure can be performed regardless the atrial anatomy. TEE provides adequate visualization of the needle and intracavitory thrombi, if present, and positioning can be precisely assessed through different projections by an expert echocardiographer. The transseptal balloon technique is relatively safe even in anti-coagulated patients. Patency of the newly created septal defect was followed up to a week after procedure, showing no decrease in size.

Supporters of balloon or blade and balloon techniques underline the importance of achieving adequate results, without the need of additional cannulae and complications of the ECMO circuit.

17.7 Transseptal Cannulation

Balloon and blade and balloon techniques have been used to effectively decompress the left heart chambers and to relieve hypertension from pulmonary circulation. Due to technical difficulties in achieving unrestricted left-to-right atrial flow, several options have been subsequently presented by different authors. In particular, addition of a transseptal cannula provides not only optimal decompression but also a potential benefit during weaning, when test-occluding the left heart cannula first allows observation of heart function.

Ward et al. [44] described a 7-Fr long introducer into the left atrium using TEE-guided transseptal puncture. The introducer was subsequently connected to the venous circuit to achieve decompression. The following techniques are very similar to this, adding an ECMO cannula to provide even better drainage.

Aiygari and colleagues [45] reviewed seven patients undergoing LA drain procedures on ECMO, focusing on procedural feasibility, complications, and success in alleviating LA hypertension. Their hypothesis was to test if percutaneous insertion of a transseptal sheath incorporated into the ECMO venous circuit was a feasible alternative to surgical venting, in draining LA. Femoral vein access was used in all patients using modified Seldinger technique. Under fluoroscopic guidance in cardiac catheterization laboratory, transseptal puncture was performed and a

transseptal sheath was positioned to be exchanged over super-stiff guidewire with a larger cannula, connected in-line into the venous limb of the ECMO circuit. Cannulae were chosen based on size and availability. Decannulation was performed bedside in the intensive care unit with manual pressure applied to site until adequate hemostasis. This resulted in prompt resolution of radiographic and echocardiographic findings of LA hypertension and left heart chamber dilation. Flow rate depends on cannula diameter and length and on LA pressure, of which only the first is to some extent modifiable. In fact adequate sizing of LA drain to the largest possible not only allows to achieve satisfactory decompression but also seems to provide a more rapid and profound resolution of LA hypertension. Higher maximum indexed LA cannula flow over a 96 h period seemed to correlate with procedural success. Moreover, the authors suggest a minimum 8-Fr sheath in infants and toddlers, 10–12-Fr sheaths in larger children, and 14–15-Fr sheaths in adult-sized patients. This procedure represents a reasonable alternative to blade or balloon atrial septostomy, which is an independent risk factor for mortality in the creation of atrial defects [46].

Schwartz et al. [47] reported a similar technique, by advancing a percutaneous femoral transseptal cannula in the left atrium, under transesophageal echocardiography guidance in a 13 year-old patient with cardiogenic shock rescued by peripherally inserted ECMO. The transseptal cannula was connected with the venous limb of ECMO circuit as previously described by Aiyagari and colleagues. In this report, authors demonstrated an immediate benefit in terms of LA and LV decompression, with a modified technique, feasible at the bedside with transesophageal echocardiographic guidance, which further simplifies the transseptal cannulation already described under fluoroscopic guidance, without the need of transferring a potentially unstable patient. In conclusion, this technique could be considered (either fluoroscopy or TEE guided, according to expertise of single centers) in the management of any ECMO patient, showing signs of progressive LV dilatation and LA and PA hypertension, in which thoracotomy/sternotomy is not anticipated.

17.8 Percutaneous Pulmonary Artery Venting

In 1988 Kolobow et al. [48] reported, in a sheep model, effective left heart decompression with a modified Swan-Ganz catheter by causing pulmonary valve insufficiency.

Avalli and coworkers [49] described a different technique, to some extent, based on the same physiological principles, by using a 6-Fr angiographic catheter that was introduced through the right jugular vein with a modified Seldinger technique and advanced in the right pulmonary artery (Fig. 17.1). The catheter was subsequently changed over a super-stiff angiographic guidewire with a 15-Fr venous cannula, which was advanced and positioned in the common pulmonary artery. At the end of the procedure, the guidewire was removed and the cannula connected to the venous limb of the ECMO circuit. The procedure was fluoroscopy guided at the bedside.

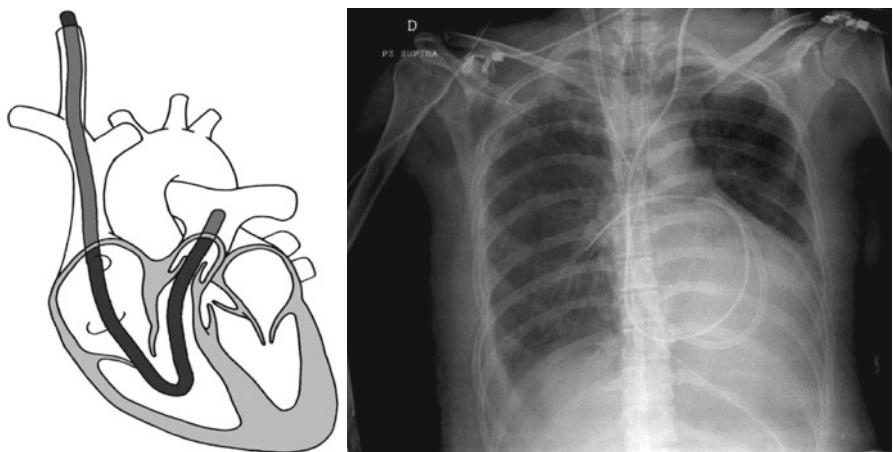


Fig. 17.1 Transpulmonary venting

Hemodynamics showed a decrease in the PA and LA pressures. At the time of weaning, the cannula was withdrawn to the superior vena cava and subsequently removed. No issues were reported in maintaining proper positioning of the venting cannula in place. Modified pulmonary cannulation offers several advantages over the previously mentioned methods: in fact surgical or even percutaneous left heart decompression by septostomy may carry a high risk of bleeding (3–7 %) and damages due to the manipulation of the heart. It can be accomplished at bedside and it is far less expensive and easier to place and manage than axial flow pumps, which will be discussed further in the appropriate section. Our group privileges this technique over the others, due to its relatively lower invasiveness and the practical advantages in performing the venting at bedside anytime with minimal patient preparation, lower cost, and steep learning curve of the trained personnel.

17.9 Transaortic Catheter Venting

Possibility exists also to directly drain left heart chambers. Fumagalli et al. [50] reported draining blood from the LV, through a percutaneously placed transaortic cannula, pumping directly into the femoral artery, with a normalization of left heart filling pressures, and resolution of pulmonary edema, as a bridge to heart transplantation.

Several experimental animal models reported a significant reduction of LV preload, in peripherally inserted ECMO, comparing pre- and post-transaortic cannula insertion in one study [51] and a significant reduction in LV total energy and work in a second publication. The LV energetic charge was significantly increased by a combination of transaortic cannula and peripheral ECMO. A third study compared four different conditions: baseline, during isolated ECMO, ECMO with transaortic venting cannula, and a combination to the previous two with IABP, showing that venting reduced LV energy and work, compared with other techniques alone [52].

17.10 Impeller Pumps

The Impella is a minimal intra-aortic impeller blood pump, a form of minimally invasive LV assist device (LVAD) that can be used to support the cardiogenic shock patient in the short and medium term. It can be positioned in the LV, via open chest, but also advanced through the femoral artery over a guidewire until reaching its definitive position. It is designed as a support device, but several works report its use as an adjunctive mechanical support for ECMO patients, in which LV decompression is indicated. Its main effects can be summarized as follows: it directly unloads the LV and it reduces myocardial workload and oxygen consumption while increasing cardiac output and coronary and end-organ perfusion. Chaparro and colleagues [53] reported for the first time the use of combined Impella and ECMO for biventricular and respiratory failure, as a bridge to recovery, in a myocarditis patient. Beuthered et al. [54] also reported the case of a 34-year-old woman with fulminant myocarditis needing ECMO support and subsequently an Impella device to decompress the LV, for acute pulmonary edema. Although reporting effective unloading of the LV, the paper also underlines the occurrence of Impella pump failure, to underline technical challenges in managing complex mechanical assistance. Koeckert et al. [55] reported successful use of Impella device for ECMO complicated by pulmonary edema, with weaning for myocardial recovery. Vlaessels [56] also reported similar combination in a pediatric patient with congenital cardiomyopathy. Interestingly, the procedure was echocardiography guided.

17.11 How to Assess Effective Decompression?

There is no established gold standard to evaluate optimal LV decompression.

In literature, the most frequently assessed parameters include echocardiographic inspection of the heart chamber size, aortic valve opening, and Doppler evaluation of flow velocities. Most often, published literature reports effective LV decompression clinical resolution of symptoms, such as disappearance of pulmonary edema and hemoptysis and preload pressure reduction. This represents the clinical goal that is desirable to achieve. We will not further discuss hemodynamic monitoring but refer the reader to the specific section.

Nonetheless, it is worthwhile to mention the possibility of TEE evaluation of the proximal part of left coronary arteries and estimation of blood flow velocity in the left anterior descending (LAD) coronary artery, by means of pulsed Doppler. The left main is visualized as an echo-free space, by placing the transducer just above the aortic leaflets, with adjustments needed to fully visualize the length of the vessel. Once the Y-shaped bifurcation between LAD and circumflex artery is visualized, coronary blood flow velocity can be evaluated by pulsed Doppler. There are no reports, to our knowledge, of this technique applied to ECMO patients. Although coronary arteries might be more challenging to visualize due to chamber decompression, still an attempt to visualize non-pulsatile or pulsatile (especially in combination with IABP or native valve opening) flow on the left main coronary artery may be useful to assess perfusion of a recovering heart.

Although the measurement of cardiac biomarkers may seem appealing to evaluate LV rest and unloading as well as to prognosticate outcome, Luyt et al. [57] reported that serial measurement of N-terminal fragment of the B-type natriuretic peptide and troponin I-C and midregional fragment of the proatrial natriuretic peptide, proadrenomedullin, and copeptin have no role as prognostic markers in refractory cardiogenic shock patients rescued by ECMO.

In conclusion, a combination of clinical and radiographic resolution, hemodynamic parameters, and standard echocardiography is up to the present days the standard to evaluate effective LV rest and decompression.

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Weaning from Extracorporeal Circulatory Support

18

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18.1 Introduction

Extracorporeal membrane oxygenation provides effective circulatory support while waiting for cardiac recovery in patients with potentially reversible heart disease, or for heart transplantation, or for implantation of a ventricular assist device (VAD) in patients with terminal heart disease [1–4].

Finding the optimal time for weaning patients from extracorporeal support is one of the greatest challenges in ECMO management. Given the potential risk of ECMO-related complications (bleeding, limbs ischemia, neurological complications, organ hypoperfusion, infections), early identification of weanable/not-weanable patients is a target of the clinician in order to achieve decannulation or indication to long-term assistance as soon as possible.

Many studies report that ECMO duration and any related complication are predicting factors of postweaning mortality [5, 6]. To identify potentially weanable patients soon would be of the greatest importance in order to limit the duration of futile assistances and direct patients to transplant lists or long-term assistance program without other additional failures or infective complications. Clear strategies to optimize outcomes and minimize futile support have not been established.

18.2 Predictors of Successful Weaning

The original indication to ECMO and the individual patient's conditions should guide the strategy and optimal time for weaning. Clinical, hemodynamic, and Doppler-echocardiographic parameters are evaluated at least on a daily basis and

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contribute to the decision of whether and when to perform a weaning trial. The search for predictors of successful weaning from ECMO combines different strategies.

18.2.1 Biomarkers

No prognostic cardiac markers of myocardial recovery are established in patients with refractory cardiogenic shock requiring circulatory support. Luyt et al. [7] recently found that NT-proBNP, TnIc, MR-proANP, proADM, and copeptin levels are high in patients with refractory cardiogenic shock requiring ECMO support, but their kinetics during the first week of ECMO support are not predictive of cardiac recovery. Moreover, there are many noncardiac reasons for cardiac biomarkers concentrations rise in ICU patients: sepsis with or without shock, other non-cardiogenic shock, and multiorgan failure (MOF) with cardiac involvement.

Blood lactate levels are considered a good indicator of organ perfusion. With regard to ECMO in the literature, different and sometimes contradictory interpretations of the values of blood lactate are reported [3, 8–10]. Low arterial blood pH value and high lactates are described as independent risk factors for mortality after extracorporeal CPR using ECMO, which most likely mirrors a longer duration of low cardiac output before ECMO initiation [11].

However, we judge reasonable to monitor the kinetic of cardiac biomarkers in patients requiring ECMO for ischemic heart disease or myocarditis and start the weaning trial after the drop of the cardiac biomarkers. Besides this we routinely monitor blood lactate levels and SvO_2 during the weaning trial as indexes of the adequacy of oxygen delivery (DO_2) related to oxygen uptake (VO_2).

18.2.2 Echocardiography

Echocardiography plays a fundamental role throughout the entire journey of a patient on ECMO and helps in monitoring cardiac recovery and the feasibility of weaning from ECMO support [12].

Daily evaluation by echography provides the physician with information about myocardial contractility, diastolic function, valvular abnormalities, and pericardial effusions; this information helps in identifying the appropriate time for a weaning trial and may alert on “problems” that must be faced and solved before the attempt of flow reduction such as tamponading effusions or valvular abnormalities.

During a weaning trial, echocardiography can confirm hemodynamic and clinical parameters that indicate a good response; even more important, echo may be the only monitoring method able to explain the mechanisms of weaning failure and to evaluate cardiac response to therapeutic interventions (Table 18.1).

As shown by Combes and colleagues, some Doppler echocardiography parameters discriminate weaned and not-weaned patients better than any other parameter

Table 18.1 Echocardiographic findings in difficult weaning

Right vs left ventricular failure
Systolic vs diastolic dysfunction
Regional wall motion abnormalities
Severe postischemic mitral regurgitation
Dynamic outflow tract obstruction
Pericardial tamponade
Pulmonary hypertension
Hypovolemia

tested. In their study, all weaned patients had a left ventricular ejection fraction greater than 25–30 %, an aortic velocity time interval above 12 cm, and a lateral mitral annulus peak systolic velocity above 6 cm under minimal ECMO flow support [13].

In Table 18.2 we report recent studies describing the outcome of ECMO-assisted refractory cardiac shock.

18.3 Technique

Criteria for weaning depend on the indication for ECMO. Obviously, the initial cause of cardiogenic shock should have been solved, and adequate time for myocardial rest and recovery must be guaranteed.

In postcardiotomy patients, suffering from postoperative myocardial stunning, some improvement of ventricular function should be evident within 72–96 h of support. In patients with myocarditis, ventricular recovery sufficient for a weaning trial from mechanical support may necessitate a longer period (2–3 weeks, depending on the etiology).

A lot of authors agree that the weaning strategy should be individualized for each patient and generally not attempted before 24–48 h of support.

Frequent assessments of clinical status and hemodynamic parameters are mandatory while on ECMO.

When a patient has stable hemodynamics with or without inotropes or IABP for more than 24 h without the need for relevant interventions and echocardiography shows a sufficient ventricular recovery, a weaning attempt can be made.

Weaning is achieved by progressively reducing pump blood flow; doing so, hemodynamic conditions change with an increase in preload and a decrease in afterload, thus resulting in rising stroke volume and cardiac output.

General criteria that must be fulfilled to start a weaning trial are the following:

- Mean arterial pressure >70 mmHg
- Low vasopressor requirement (inotropic score less than 10)
- $\text{SpO}_2 >95\%$
- $\text{ScvO}_2 >70\%$
- Adequate natural lung oxygenating ability (chest X-ray improving after acute pulmonary edema)
- Improving 2D echo with EF >25–30 %

Table 18.2 Recent studies describing the outcome of ECMO-assisted refractory cardiac shock

		% of successful weaning	Mortality	Conclusions/comments
Unosawa et al. [5]	61.7 % Mean ECMO duration 64 ± 62 h	66 % at 30 days (tot) (51.7 % in ECMO weaned) 70.2 % at 1 year 82.4 % at 5 years		Incomplete sternum closure predicts mortality during ECMO; intraoperative CPB time is significantly different among W/NW ECMO >48 h is a predictor of mortality post weaning; age, preop-LVEF, EuroSCORE, duration of ECMO, and peak creatine level during ECMO are significantly different among W/SWNs
Slottosch et al. [6]	62.3 % Mean ECMO duration 79 ± 57 h	70 % at 30 days (tot) (52.1 % in ECMO weaned)		Predictors of mortality: age, lactates at 24-h ECMO, duration of ECMO support, GI complications, any ECMO-related complication
Aissaoui et al. [13]	40 % (+12 pts bridged to VAD/transplant)			Echographic predictors of successful weaning: LVEF >20–25 %, aortic VTI ≥ 10 cm, mitral annulus peak systolic velocity TDSa ≥ 6 cm/s at minimal ECMO flow
Chang et al. [14]	(only weaned pts)	26 % in-hospital		Predictors of in-hospital mortality: MAP and SOFA score (cutoff value 13) on the day of ECMO removal, daily urine amount on the second day after weaning
Formica et al. [15]	69 % Mean ECMO duration 190 ± 127 h	47.6 % at 30 days 61.9 % in-hospital		Blood lactate levels at 48 h of ECMO support and number of PRBCs transfused are associated with 30-day mortality
Rastan et al. [16]	63 % (+20 pts bridged to VAD/transplant) Mean ECMO duration 79 ± 68 h	75.2 % in-hospital 82.4 % at 6 months 83.5 % at 1 years 86.3 % at 5 years (20 pts bridged to VAD/transplant)		Predictors of in-hospital mortality: age, diabetes, preoperative chronic kidney disease, obesity, lactates, EuroSCORE >20 %
Luo et al. [10]	60 % (+5 pts bridged to transplant) Mean ECMO duration 126 ± 104 h	42 % in-hospital (5 pts bridged to transplant)		CRRT on ECMO is a predictor of mortality No significant difference between ECMO and ECMO + IABP

Bakhtary et al. [3]	55 % (+7 pts bridged to VAD/transplant) Mean ECMO duration 154±108 h	53 % at 30 days 71 % in-hospital 78 % at 3 years	Predictors of hospital survival: absence of pulmonary hypertension, absence of diabetes, use of IABP
Chen et al. [8]	69.4 %	66.7 % in-hospital (tot) (52 % in ECMO weaned)	S vs NS have lower inotropic score, reduced blood lactate level, shorter CPR duration, surgical revascularization, reduced SOFA score
Zhang et al. [17]	43.7 % Mean ECMO duration 65 ±41 h	68.75 % at 30 days 75 % in-hospital	Preop-LVEF and lactates, CK-MB, and CK-MB/TOT CK at 48-h ECMO are significantly different among W/NW pts CK-MB/TOT CK at 48-h ECMO predicts mortality on ECMO
Doll et al. [18]	61 % (+12 pts bridged to VAD/transplant) Mean ECMO duration 62 ±53 h	76 % at 30 days 82 % at 5 years	Higher mortality for CABG + aortic valve replacement vs other surgery Predictors of in-hospital survival are younger age, absence of preoperative AMI, absence of DM, use of IABP
Smedira et al. [4]	35 % (+48 pts bridged to transplant)	24 % at 3 days 62 % at 30 days (tot) (48 % in ECMO weaned)	Risk factors for mortality: age, thoracic aorta surgery, reoperation, nonuse of IABP
		76 % at 5 years (tot) (40 % in ECMO weaned)	(48 pts bridged to transplant)

W weaned patients, NW not-weaned patients, S survivors, NS nonsurvivors, WS weaned and survived, WNS weaned but not survived (died after ECMO)

Our weaning strategy follows a step-by-step approach. Doppler echocardiography is repeated at each ECMO flow level and cardiac function is continuously monitored through a Swan-Ganz catheter.

Ventilatory support is augmented progressively during the weaning to face the progressive rise in pulmonary blood flow.

The weaning protocol consists in the reduction of ECMO pump flow in steps of 0.5 L down to 1.0 L/min. This flow is maintained for about 40–60 min after having obtained an ACT of 180–200 s. A failure in cardiac output rise, with high filling pressures and signs of inadequate peripheral perfusion (rise in blood lactate levels, significant reduction in SvO_2), associated with echographic findings of ventricular insufficiency leads to restore full assistance waiting for further possible recovery.

When hemodynamic parameters remain stable without the addition of inotropes or with low level of inotropes and the patient's LVEF is greater than 20–25 % with normal right ventricular TAPSE, adequate cardiac index ($\text{CI} > 2.2 \text{ L/min/m}^2$), wedge pressure $< 18 \text{ mmHg}$, and central venous pressure $< 15 \text{ mmHg}$, ECMO removal is considered. Heparin infusion is stopped and pump flow is raised in order to avoid clot accumulation on the membrane. At normal coagulation and platelet count, ECMO circuit is clamped and decannulation is performed at the bedside except for central or surgical cannulation where the procedure is performed in the operating room.

Levosimendan is frequently administered at our institution to facilitate the weaning process. Its peculiar characteristics make it a promising drug in this setting: it improves both systolic and diastolic function without altering the myocardial oxygen balance and reduces afterload and inflammatory response [19–22]. Although no prospective observations have been published to date – to our knowledge – on the use of levosimendan in this specific condition, our preliminary results suggest a potential beneficial role of this drug in restoring cardiac output and improving endothelial function [23]. Levosimendan has hence become part of our weaning protocol and is nowadays employed in most patients with an alteration in cardiac function. It is infused at an average dose of 0.1 mcg/kg/min for 24 h, and weaning is attempted thereafter.

When intracerebral hemorrhage or brain death occurs, extracorporeal support can be sustained if the patient is a potential organ donor to allow organ support and is withdrawn in other cases.

18.4 After Weaning

After successful weaning from ECMO support, patients need strict monitoring of vital parameters to ensure cardiac output adequacy in the long term.

Continuous monitoring of cardiac output, SvO_2 , lactate levels, acidosis, urine output, and peripheral perfusion is mandatory for the first 24–48 h after decannulation.

Signs of low cardiac output syndrome must be quickly identified and prompt therapeutic interventions carried out. Inotropic support may need to be optimized; again, echography is fundamental in this phase.

In case of extreme hemodynamic instability, with new onset of cardiogenic shock, reimplantation of extracorporeal support must be considered.

In the first hours after decannulation, a systemic inflammatory response may be evident, with tachycardia, fever, and hypotension; volume expansion and vasopressors are often required.

In the subsequent days, if the course in the immediate after-weaning period was regular, optimization of cardiologic therapy is the challenge. Periodic echographic assessments of post-recovery LVEF, diastolic function, valvular defects, and pericardial effusions are performed.

When left ventricular function remains severely impaired after successful ECMO weaning, cardiac resynchronization therapy (CRT) must be considered [24, 25].

In peripheral ECMO, post-decannulation complications related to the presence of cannulas may be evident or may need appropriate investigation by Doppler echography. We also suggest to routinely inspect cannula insertion sites to uncover wound infectious complications.

18.5 Failure to Wean

Sometimes ECMO weaning is deemed impossible. When in the course of extracorporeal support, the impossibility to wean the patient becomes clear, prompt identification of patients amenable to long-term support or transplantation is mandatory, in order to prevent further organ dysfunction and infections and to direct patients to these treatments. In these patients VADs can be considered either as “bridge” to transplantation or as “destination” therapy.

In the last years, mechanical circulatory support devices have evolved into advanced easy-to-implant and easy-to-use devices, capable of reversing low cardiac output syndrome in an “exit” strategy tailored specifically to each patient. Selection of the appropriate device should take into account residual cardiac function and the presence of left/right or bi-ventricular failure and underlying comorbidities. These specific issues are addressed elsewhere in the book.

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Treatment Options for End-Stage Cardiac Failure

19

Gurmeet Singh

19.1 Introduction

Preceding chapters have reviewed extracorporeal membrane oxygenation (ECMO) support of cardiogenic shock in detail. Cardiogenic shock is associated with significant morbidity and mortality. Rapid intervention and resuscitation are essential. Expedited management requires suitable support technology and a clearly delineated plan of action. This section will discuss alternative mechanical strategies and technologies that have emerged to support cardiac failure. Mechanical circulatory support (MCS) augurs a maturing frontier with the potential to inexorably alter the future of heart failure management.

Rapid evolution and adoption of novel devices, along with global variations in practice and device availability, limit any review from being comprehensive and current; instead, this chapter will focus on general principles, with selected illustrative examples.

19.2 INTERMACS Classification

The New York Heart Association functional classification insufficiently discriminates between varying degrees of advanced heart failure (HF). Accordingly, the Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) has proposed distinct patient profiles to differentiate stages of advanced HF [1].

INTERMACS is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and represents a collaborative database effort between the NHLBI, the US Food and Drug Administration (FDA), and the Centers for Medicare &

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Table 19.1 INTERMACS patient profiles (after Stevenson) [1]

INTERMACS profile	Short description
1	Critical cardiogenic shock
2	Progressive decline on inotropes
3	Stable, but inotrope dependent
4	Symptoms at rest; home on oral therapy
5	Exertion intolerant
6	Exertion limited
7	Advanced NYHA class III symptoms

Medicaid Services [2, 3]. This North American registry accounted VAD implants in nearly 6,900 patients from 145 participating sites in the fifth INTERMACS annual report [2].

Hospitalized patients are categorized as follows: INTERMACS 1 profile patients (Table 19.1) are the most severely decompensated, in critical cardiogenic shock; level 2 patients are those experiencing progressive decline on inotropes; and profile level 3 is defined as hemodynamically stable, but inotrope dependent.

Not surprisingly, preoperative severity of cardiac decompensation correlates with outcomes following MCS. INTERMACS profile levels 1 and 2 have the poorest survival – approximately 5–8 % lower. Overall, actuarial survival is 80 and 70 % at 1 and 2 years, respectively [2]. With recognition of suboptimal outcomes for profile level 1 patients, combined with improving technology, increasingly earlier VAD implantation is being performed. At present, INTERMACS level 1 patients account for 16.6 % of new implants [2].

It is anticipated that as more devices receive approval and wider adoption, the ability to track trends in MCS will provide further insights and guide future care. Efforts are underway to consolidate data into a single registry – the International Society for Heart & Lung Transplantation (ISHLT) Mechanical Assisted Circulatory Support (IMACS) Registry [4].

19.3 Intra-aortic Balloon Pump (IABP) Counterpulsation Therapy

IABP therapy has been employed since Kantrowitz's initial publication in 1968 [5]. The success, combined with relative speed of insertion and simplicity of the IABP, has led to it becoming the most widely used initial assist device.

The IABP is a helium-filled balloon affixed to the tip of a catheter, generally inserted retrograde through the femoral artery. The tip of the balloon is optimally positioned 1–2 cm distal to the origin of the left subclavian artery. The IABP operates on a volume-displacement counterpulsation principle to exert its hemodynamic effect. Thus, the balloon inflates in diastole and deflates in systole.

Physiologically, the IABP augments coronary perfusion, reduces left ventricular afterload, and reduces left ventricular wall tension. Diastolic inflation increases

coronary perfusion pressure and coronary blood (and hence oxygen) supply. Increased diastolic pressure may improve coronary collateral perfusion, as well as systemic perfusion.

Systolic deflation just prior to isovolumetric contraction results in afterload reduction, reduced LV wall tension, increased stroke volume, and cardiac output augmentation. Management with IABP requires appropriate timing to adjust inflation and deflation, guided by the arterial pressure waveform. Modern devices are substantially automated, simplifying monitoring and timing.

Indications for IABP include cardiogenic shock, coronary ischemia, and dysrhythmias. Complications post-myocardial infarction can also be supported, such as ventricular septal defects (VSDs), acute severe mitral regurgitation secondary to papillary muscle rupture, and left ventricular aneurysms.

IABP use is absolutely contraindicated in aortic insufficiency and aortic dissection. Caution must be advised in patients with severe atherosclerotic disease, significant peripheral vascular disease, abdominal aortic aneurysm, and graft replacement of the iliac or femoral arteries.

For patients in extremis, IABP may be insufficient to support severe dysrhythmias or the degree of hemodynamic embarrassment. Additionally, immobilization of the patient, combined with peripheral arterial access, limit the effective duration of support. Hemolysis and platelet consumption may also occur.

The hemodynamic benefits of IABP support have been reported to improve survival in cardiogenic shock following acute myocardial infarction (MI) [6]. The joint American College of Cardiology (ACC) and American Heart Association (AHA) guidelines have assigned IABP a class IIa recommendation as a management option in this scenario [7]. European guidelines suggest consideration of IABP in this situation as a class IIb recommendation [8]. Previous international guidelines had supported IABP usage as a class I indication for post-MI shock, but recently IABP efficacy has been questioned in the IABP-SHOCK II trial [9, 10]. Nevertheless, previous widespread adoption and clinician comfort with IABP mean it currently remains a first-line management tool for hemodynamic support.

19.4 Percutaneous Mechanical Circulatory Support

IABP limitations, combined with invasiveness of traditional surgical ventricular assist device placement, have stimulated the development of percutaneous mechanical circulatory support (MCS). Impella® (Abiomed, Danvers, Massachusetts, USA) and TandemHeart® (CardiacAssist, Inc., Pittsburgh, Pennsylvania, USA) are prototypical devices in this category.

Advantages of percutaneous MCS include deployment without the traditional surgical approach, thus sparing operating room resources and time, relative simplicity of insertion, and ability to rapidly institute mechanical assistance, thereby expediting resuscitation.

The Impella® consists of a micro-axial pump mounted on a 9 French catheter. The device is situated in the left ventricle, having crossed the aortic valve. Blood is

drawn into the pump through an inlet, and then ejected beyond the aortic valve through an outlet, into the ascending aorta. An external console controls and monitors speed and pressure measurements, ensuring appropriate pump function.

Multiple configurations of the Impella® are available. Currently, the 2.5 (2.5 lpm, 12 French pump) and CP (14 French pump) are percutaneously insertable. The 5.0 (5.0 lpm, 21 French pump) and LD (left direct – 5 lpm, 21 French pump) require a surgical approach. The 5.0 is inserted via a graft anastomosed to the femoral or axillary artery, while the LD is placed through a graft sewn on the ascending aorta and directly inserted in LV.

The Impella® 2.5 is unlikely to provide sufficient decompression and cardiac output for the severest cases of cardiogenic shock and postcardiotomy shock (PCS). The Impella-EUROSHOCK Registry found a greater than 64 % 30-day mortality in post-myocardial infarct cardiogenic shock supported with Impella® 2.5 [11]. The Impella® 5.0 and LD, however, have shown some potential utility in the PCS cohort [12].

Contraindications to insertion of this device include presence of a mechanical prosthetic aortic valve, significant aortic stenosis, aortic regurgitation, atherosclerotic aortic, and left ventricular (LV) thrombus [13]. Complications particular to this pump to consider include arrhythmias, aortic insufficiency, LV perforation, lower extremity ischemia, and pump migration. Hemolysis and intraventricular thrombosis have also been reported with Impella® usage [14–16].

The TandemHeart® system consists of a paracorporeal centrifugal pump, requiring only 10 ml priming volume, a transseptal left atrial cannula, and a femoral arterial cannula. Thus, left atrial to femoral artery bypass is accomplished, entirely percutaneously. This system is able to deliver up to 4–5 lpm cardiac output while decompressing the left heart [17, 18]. Utility of this system has been reported in a variety of clinical scenarios, achieving satisfactory hemodynamic support [19]. The interatrial septal puncture does not require closure – although it is surgically repaired if the patient is transitioned to long-term VAD. While device insertion is performed in the cardiac catheterization lab, the TandemHeart® is removable at the bedside.

Significant aortic insufficiency is a contraindication to specifically employing the TandemHeart®. Device-specific complications include lower extremity ischemia, cannulae migration, persistent atrial septal defect, and left atrial perforation [13].

19.5 Short-Term Ventricular Assist Devices (VADs)

Decisions regarding MCS implantation can be challenging for INTERMACS profile 1 or 2. Time limitations based on critical clinical conditions may not permit detailed evaluation to determine long-term MCS or transplantation suitability. Short-term VADs are an appropriate “bridge to decision” strategy, whereby a trial of MCS may provide an opportunity to ascertain end-organ dysfunction reversibility, especially if neurologic status is unclear. This is particularly applicable for postcardiotomy shock (PCS), cardiac arrest scenarios, or cardiac catheterization lab support. Historically dismal PCS outcomes have improved substantially with VAD support [20].

The ideal short-term VAD should be relatively inexpensive and capable of rapid, easy deployment. Simplicity of management is also desirable. Percutaneous devices fulfill these requirements. Currently, these devices have limitations with duration of support. Patient immobility is another consideration. Most importantly, however, the option to readily provide biventricular support is desirable. Right ventricular percutaneous support systems are still under development and evolution. Additionally, percutaneous VAD support systems are suboptimal choices for more intermediate durations of support.

At the Mazankowski Alberta Heart Institute, we employ the CentriMag® (Thoratec®, Pleasanton, California, USA) paracorporeal support system. This device provides the option to provide isolated left or right ventricular assistance or biventricular support [21–24]. Takayama et al. have described a percutaneous strategy for deploying the CentriMag® as an RVAD [25].

When cannulating the patient centrally, the cannulae are tunneled and exit through the anterior abdominal wall. The actual pump rests within a bearingless motor, connected to the drive console. We have also successfully employed a temporary in-line oxygenator when hypoxemia is not manageable with mechanical ventilation alone. As pulmonary edema resolves, and hypoxemia improves, the oxygenator can be readily removed from the circuit.

The CentriMag® system is magnetically levitated, bearingless, and capable of generating up to 10 l/min of flow at a maximum of 5,500 rpm. Without bearings, regions of blood stasis and friction, thermal damage, hemolysis, and thrombus formation are reduced [22].

Temporary VAD implantation is recommended (class IIa) for patients in cardiogenic shock with end-organ compromise or unclear transplant eligibility status, who have a reasonable expectation to improve with restoration of good hemodynamics [26].

19.6 Long-Term VADs

For long term destination may be considered as a bridge to transplant, bridge to candidacy, bridge to recovery, or for long-term/destination therapy. Increasingly, patients may migrate between these broad categories, based on medical status, personal preference, and technological advances. Early referral for VAD is always preferable. Suitable candidate selection requires recognition of patients too ill to benefit, balanced against situations where patients are not ill enough.

Currently, implantable continuous-flow pumps have supplanted volume-displacement (pulsatile) devices in most adult assist device programs. Continuous-flow devices are quieter, have greater ease of implantation, and are of significantly smaller size. Continuous-flow ventricular assist devices (CF-VADs) still require anticoagulation, typically with warfarin and ASA. Patients bridged to heart transplantation with CF-VADs have similar posttransplant survival at 1 and 3 years (87 and 82 %, respectively) compared to non-LVAD-bridged recipients not on inotropic support (88 and 82 %) [27].

With respect to long-term implantation, when compared to pulsatile devices, continuous-flow LVADs, CF-VADs, have been shown to have better outcomes with respect to stroke and 2-year survival [28]. Besides better device durability, CF-VADs also have 50 % fewer device-related infections [28]. CF-VADs improve both functional capacity and quality of life based on heart failure metrics [29]. Battery technology continues to improve, permitting increasing freedom for these patients. While pulsatile devices provide greater left ventricular volume unloading, there is no difference in hemodynamic support or exercise capacity based on VAD design alone [30].

The HeartMate II® (Thoratec®, Pleasanton, California, USA) axial-flow rotary blood pump is currently the most popular durable continuous-flow implantable left ventricular assist device (LVAD) and has been effective for bridge to transplant (BTT) and permanent or destination therapy (DT) [2, 31, 32]. The device currently has US Food and Drug Administration (FDA) approval for bridge to transplantation, as well as destination therapy.

An inflow cannula is inserted into the left ventricular apex, with an outflow graft anastomosed to the ascending aorta. The device is implantable and rests subdiaphragmatically either intra-abdominally or in the pre-peritoneal space of the left upper quadrant. Blood leaves the left ventricle and enters the pump through an inflow conduit. An electric motor drives a permanent magnet, the rotor. As the rotor spins, blades propel blood through the outflow graft back into the ascending aorta. The HeartMate II® is an axial-flow pump; that is, blood flow enters and exits parallel to the pump axis.

The rotor spins on bearings, capable of generating as much as 10 l per min blood flow, functioning in parallel with the patient's circulation. Clinicians set a fixed speed for the pump, generally between 8,000 and 10,000 revolutions per minute (RPM), and actual flow depends upon various factors, including patient afterload, pump speed, and power provided to the motor. A system controller, worn around the patient's waist, is connected to the pump by a transcutaneous driveline and regulates device function. Portable batteries allow patients to mobilize untethered [33].

Long-term implantation with this rotary device has been shown to have fewer complications, improved survival, better quality of life, and improved functional capacity compared to a pulsatile VAD [29]. The European experience with this device has demonstrated similar excellent outcomes and durability for long-term support [34]. Destination therapy patients have improving 1-year survival, around 74 % [32].

Our center also employs the HeartWare® ventricular assist system (HVAD®) (Framingham, Massachusetts, USA). The HeartWare® device currently has FDA approval for bridge to transplant indications. This pump sits within the pericardial space. Ease of implantation is enhanced not only by eliminating the need to dissect below the diaphragm but also by simplicity of actual implant technique. Centrifugal in design, the rotor (often referred to as the impeller), is suspended by magnets and hydrodynamic thrust bearings. There are no points of mechanical contact within the pump. The pattern of blood flow is similar to that described above for the HeartMate II®: blood enters the device through an inflow cannula integrated within the pump. The suspended impeller drives blood forward, exiting via the outflow cannula and

through a graft anastomosed onto the ascending aorta. A percutaneous driveline is tunneled from the device to a controller worn around the patient's waist. Portable batteries permit patient mobility and freedom from tethering.

Blood flow is determined by impeller speed (RPMs), current (power), and blood viscosity. Typically, the device is set to operate between 2,400 and 3,300 RPM. Additionally, clinicians enter the patient's hematocrit, and blood viscosity is calculated from this value. As with the HeartMate II®, blood flows are estimated.

Typically employed as a left-sided VAD, the HeartWare® HVAD® has been implanted as an isolated RVAD [35] as well as a permanent implanted biventricular support system (BiVAD) [36, 37]. Potential use as a BiVAD is advantageous; however, quality of life is significantly different with two devices, two controllers, and two sets of batteries to manage, compared to a simple LVAD.

Potential disadvantages with the HeartWare® HVAD® device include higher recommendations for anticoagulation, along with thrombosis concerns [38–40]. Lower rates of thrombosis have been described more recently, possibly attributable to an improved LV coring tool and a sintered inflow cannula [39, 40]. HeartWare® recommends targeting a PT INR of 2–3 for the HVAD® [41], compared to a PT INR of 1.5–2.5 for the HeartMate II® [42]. Additionally, although there are considerable differences between centers and local protocols, recommendations for antiplatelet therapy are generally greater with the HVAD® than the HeartMate II® [43].

There are notable physiological differences between axial and centrifugal pumps [44]. While both types of rotary pumps are afterload sensitive, centrifugal pumps have greater afterload sensitivity compared to axial-flow devices. Centrifugal pumps also have greater flow pulsatility and higher estimated flow accuracy. During lower flow conditions, centrifugal flow devices typically demonstrate lower inlet suction.

Beyond survival, end-organ optimization and functional recovery are the goals of MCS. Patients with established renal failure who are unlikely to recover function despite improved cardiac output are not recommended as candidates for long-term devices [26]. CF-VADs enhanced functional capacity and quality of life [28] compared to pulsatile devices [45]. Health-related quality of life and functional capacity assessment, rather than survival, are increasingly pertinent. Improved understanding of these factors may be useful in determining patient-device suitability and lifestyle modifications, and perhaps refining implantation indications [46].

Neurologic events are still reported in nearly 10 % of HeartMate II® recipients [47]. Ischemic strokes occur in 8 % of recipients, while 11 % may suffer a hemorrhagic stroke [28]. Subsequently, less aggressive anticoagulation regimens have been advocated.

Development of aortic insufficiency (AI) has been identified as an issue with continuous-flow long-term VADs. Nearly half of patients demonstrate moderate or greater AI by 18 months after CF-VAD implantation [48]. For this reason, if possible, maintaining aortic valve opening by permitting some left ventricular loading may be desirable.

Use of CF-VADs has uncovered a specific hemodynamic and hematologic constellation that can result in hemorrhage in 25 % of patients [49]. Significant epistaxis is an etiology in one-fifth of cases [49]. Gastrointestinal bleeding is

common – over 20 % – following CF-VAD implantation [50, 51]. Angiodysplasia and arteriovenous malformations (AVM), coupled with anticoagulation, acquired von Willebrand factor (vWF) deficiency, fibrinolysis, and reduced platelet numbers with impaired function, all contribute to bleeding [52–55].

Two mechanisms are proposed to explain AVM. Firstly, it is postulated that increased intraluminal pressure and vascular smooth muscle contraction results in increased smooth muscle tone and vessel dilation, with ensuing AVM formation. The second mechanism supposes that reduced pulse pressure results in hypoperfusion, vascular dilation, and ultimately angiodysplasia [56].

Analogous to Heyde's syndrome, the shear stress produced during CF-VAD therapy results in reduction of high molecular weight (HMW) vWF multimers [52, 57]. The pump itself may directly contribute to HMW vWF deformation and proteolysis. vWF binding to collagen or platelet gp1b receptor binding is thus impaired. Multiple mechanisms of acquired vWF deficiency have been elucidated from in vitro studies [58].

Driveline infections remain problematic: the Mayo Clinic reported a 12 % driveline infection rate, with prolonged duration of support increasing the risk [59]. Based on INTERMACS data, nearly one-fifth of patients experience a driveline infection within a year of LVAD implantation. Interestingly, younger age represents the only identifiable risk factor. Most concerning is that driveline infections may be adversely associated with survival [60].

Patient selection is becoming increasingly refined with greater clinical experience. Various scoring systems have emerged to assist clinical decision-making. Recently, the HeartMate® II Risk Score (HMRS) has been proposed as a mortality risk stratification tool for CF-VADs [61]. Patient age, serum albumin, serum creatinine, INR, and center volume are predictive factors. The Destination Therapy Risk Score (DTRS) [62] was developed during the pulsatile device era and is more complex to calculate. DTRS utility in the CF-VAD era is likely limited. MELD scoring has also been successful at predicting mortality for CF-VADs [63–65].

VAD usage as a bridge to transplantation is currently a class I recommendation for patients who have failed maximal therapy and have a high risk for mortality prior to allograft availability [26]. Early referral for VAD implantation is currently a class IIa recommended approach, as outcomes are superior prior to the patient's developing hypotension, hyponatremia, renal dysfunction, and the need for recurrent hospitalizations [26]. Increasingly outpatients are being evaluated for appropriateness of mechanical circulatory support (MCS) [66].

Patients deemed ineligible for cardiac transplantation due to pulmonary hypertension may benefit from hemodynamic unloading of the left ventricle. Coupled with aggressive medical therapy, long-term VAD often successfully bridges this patient group to transplant candidacy by reducing pulmonary artery pressures, transpulmonary gradient, and pulmonary vascular resistance [67]. The current recommendation for bridge to candidacy with long-term VAD for pulmonary hypertension related to HF is class IIa [26].

Permanent or destination therapy (DT) with a pulsatile LVAD was first demonstrated to be a feasible alternative to medical therapy for end-stage heart failure in the REMATCH trial [45]. Subsequently, it was advocated that LVAD therapy for

DT yielded better results if implantation was performed prior to development of major complications [62]. Currently, durable LVAD placement is advised (class I) for transplant-ineligible advanced heart failure patients with a high 1-year mortality risk, without irreversible end-organ dysfunction [26]. Elective implantation is also advocated over urgent VAD (class IIa) [26].

Prior to acceptance for long-term VAD implantation, a multidisciplinary team assessment (surgical, medical, nutritional, and psychosocial) is highly recommended (class I) [26]. In our experience, participation of cardiology, cardiac surgery, critical care, and a specialized VAD team has greatly improved assessment, decision-making, communication, and management.

19.7 Right Ventricular Failure (RVF)

Medical management of RVF is beyond the scope of this chapter. However, RV function is a critical consideration during MCS application. RVF is associated with higher earlier morbidity and mortality [2, 68]. Unlike venoarterial ECMO, LVADs do not directly unload the right heart. Nevertheless, following LVAD implantation, objective improvements in RV function are detectable [69]. Conversely, CF-VADs may exacerbate RVF by causing interventricular septal shift, RV distortion, and worsening tricuspid regurgitation, combined with increasing RV preload. RVF that requires temporary RVAD support may occur in up to 9 % of LVAD recipients, with an associated significantly increased mortality [70].

Predicting RV failure, therefore, has important clinical implications. The right ventricular failure risk score relies upon four variables (vasopressor usage, creatinine, bilirubin, and aspartate aminotransferase) as predictors of post-LVAD implantation RV failure [71]. A higher RVFRS was also associated with greater mortality [71]. Other investigators have reported preoperative tricuspid regurgitation as predictive of RV failure [68]. Raina and colleagues describe an echocardiographic scoring system consisting of RV fractional area change, estimated right atrial pressure, and left atrial volume index [72]. Central venous pressure (CVP) to pulmonary capillary wedge pressure ratio greater than 0.63, elevated blood urea nitrogen, and preoperative mechanical ventilation have been shown to be independent predictors of RVF following CF-VAD insertion [73]. These investigators also found elevated CVP ($>15 \text{ cm H}_2\text{O}$) and right ventricular stroke work index $<300 \text{ mmHg} \times \text{ml} \times \text{m}^{-2}$ to be predictive.

19.8 Total Artificial Heart (TAH)

TAH technology offers biventricular support in the form of an orthotopically placed device, which necessitates complete biventricular and heart valve excision [74]. The SynCardia® temporary TAH (TAH-t) (SynCardia Systems, Inc., Tucson, Arizona, USA) is a pneumatically driven, volume-displacement device, typically delivering between 7 and 9 l/min of cardiac output [75]. It has been used as a bridge to transplant with 61–87 % success rate [74–77].

There is limited clinical experience with the AbioCor® (Abiomed®, Massachusetts, USA), an entirely self-contained TAH. The internal battery is rechargeable using transcutaneous energy transmission (TET). In the USA, the device has FDA approval as Humanitarian Use Device. A next generation device is under development.

TAH is an attractive option for MCS in the setting of cardiac allograft failure, as donor graft ventricles are excised, eliminating the need for immunosuppression, and thus the associated risks of wound healing and sepsis [78, 79]. Other unique clinical scenarios where TAH support is potentially advantageous include post-infarct ventricular septal defect [75, 80] and massive myocardial infarction/necrosis. Furthermore, in patients requiring biventricular support as bridge to cardiac transplantation, TAH had a significantly lower stroke rate and a trend toward improved survival when supported for greater than 90 days [81].

Currently, limitations of TAH technology include device size and complication rates.

19.9 Transplantation

The gold standard treatment for end-stage heart failure remains cardiac transplantation. Graft durability, however, remains limited by accelerated cardiac allograft vasculopathy (CAV). Median recipient survival remains 10 years [27]. Additionally, the organ supply-demand discrepancy continues to grow. Since 1998, less than 4,000 heart transplants have been reported per annum to the International Society for Heart & Lung Transplantation (ISHLT) Registry, and these data probably represent two-thirds of heart transplants performed globally [27]. Interestingly, 36 % of heart transplant recipients are currently bridged with MCS [27].

Besides limited donor organ availability, post-transplantation challenges exist. Prolonged immunosuppressive therapy is required. Donor right heart failure following transplantation remains a significant concern due to its frequency and association with poor outcomes. In the first 3 years following cardiac transplant, graft failure and infection represent the most common causes of death. Beyond 3 years, malignancy and cardiac allograft vasculopathy contribute to mortality [27].

Refractory, end-stage heart failure patients are recommended for cardiac transplant referral [81]. Patients in cardiogenic shock with documented inotropic dependence, peak VO₂ (oxygen consumption) less than 10 ml/kg/min, severe symptomatic ischemic heart disease not amenable to revascularization, and refractory ventricular arrhythmias are all suitable cardiac allograft candidates [82]. Additionally, patients on MCS with device-related complications should be advanced for transplantation. Canadian Cardiovascular Society guidelines recommend MCS for cardiac transplant candidates who clinically deteriorate or are unlikely to survive until a suitable donor organ becomes available [83].

Decisions to proceed with listing for transplantation may be aided by an estimation of mortality risk. Adjudging heart transplant candidacy in ambulatory patients

includes measuring VO₂, calculating the Heart Failure Survival Score, and employing the Seattle Heart Failure Model [84].

Heart transplantation is contraindicated for patients with active malignancy or infection, as both conditions may be exacerbated by immunosuppression. Pulmonary hypertension heralds poor outcomes following transplantation. Pulmonary vascular resistance (PVR) >5 Wood units or a trans pulmonary gradient (TPG) ≥15 mmHg are contraindication to cardiac transplantation [85]. European guidelines suggest that a PVR >4–5 Wood units and a transpulmonary gradient >15 mmHg are contraindications [86].

Recently, the Columbia group has published the CARRS prognostic scoring system to predict survival in high-risk transplant candidates. CARRS incorporates cerebral vascular accident, serum albumin, retransplantation, renal dysfunction, and >2 prior sternotomies as risk factors. They found that a high score was predictive of poorer survival [87].

Currently, over one-third of patients are bridged by MCS to heart transplant [27]. Of the current MCS options, LVAD support as a bridge to transplant provides the best outcomes [88]. It is recognized that cardiac transplantation for INTERMACS 1 and 2 patients is associated with poorer outcomes than bridging with MCS. Attisani and colleagues reported 42.3 % early mortality for INTERMACS profile 1 and 2 patients undergoing urgent cardiac transplantation versus 4.3 % for emergent MCS insertion [89]. The Spanish National Heart Transplant Registry database was recently examined and the investigators demonstrated that INTERMACS profile correlated with outcomes following emergency heart transplantation: postoperative mortality was 43 % in profile 1 patients and 26.8 % in profile two recipients [90].

Enthusiasm for a possible future with limitless donor organs was fostered by the clinical case of baboon-to-human cardiac xenotransplantation in 1985 – “Baby Fae” [91]. The eagerness for cardiac xenotransplantation, however, abated following recognition of the potential for xenozoonoses, with an unknown actual transmission risk [92]. Furthermore, immunologic barriers have not been overcome, and primary graft dysfunction following cardiac xenograft remains a challenge [93].

Globally, insufficient access to donor organs exists to meet the demand for heart transplantation. Additionally, in the MCS era, some patients decline the opportunity for a heart transplant once they have become accustomed to improved quality of life compared to their previous existence. The evolution of VAD technology in the continuous-flow era has led to the suggestion that long-term mechanical assist device support outcomes are rapidly becoming on par with heart transplantation [94].

As patient selection and technology are refined, risks and complications will be further reduced, and MCS may become preferred to heart transplantation in certain scenarios. Since cardiac allografts have a finite lifespan – median recipient survival of 10 years – it may be more desirable to perform VAD implantation in young patients, with device replacement as required, reserving the limited donor cardiac grafts until later in the course of the disease process or until needed to overcome device-related complications.

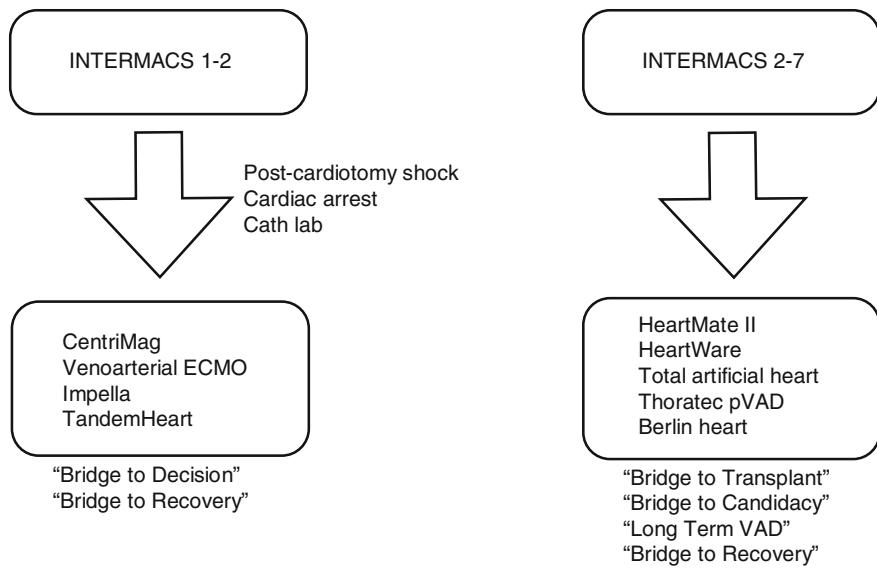


Fig. 19.1 Mechanical circulatory support (MCS) algorithm based on INTERMACS profile level

19.10 Algorithm

The key to salvageability is early, expeditious intervention. The Minnesota program has described their bridge to decision approach for refractory cardiogenic shock patient with multiple organ dysfunction [18]. They employ CentriMag® BiVAD support and reevaluate future decisions based on end-organ recovery, neurologic status, and cardiac recovery.

Figure 19.1 outlines a proposed algorithm for device selection based on INTERMACS profile level and clinical scenario. Since clinical status determines patient categorization, migration between categories is common. Accordingly, a “bridge to bridge” strategy may also be employed. For example, VA ECMO may be used as bridge to a short-term device, which could in turn serve as a bridge to decision.

19.11 Future Considerations

Improving devices with fewer complications may make VAD therapy more attractive to medically managed advanced HF patients. Accordingly, the Medical Arm of INTERMACS (MEDAMACS) is collecting data on medically treated patients who have the potential to require VAD therapy [2]. The registry was launched in January 2013, with an intention to focus on INTERMACS profile levels 4–6.

HLA sensitization has become an increasingly important challenge facing VAD recipients. Donor availability and posttransplant outcomes may both be affected. Induction of sensitization is complex, with various mechanisms proposed [95].

Highly anticipated future developments include further improved quality of life with greater battery life and less tethering. Transcutaneous energy transfer (TET) would substantially improve quality of life for patients by eliminating tethering. Pocket-sized controllers are already available. Additionally, new convenient approaches to biventricular support are expected to emerge.

19.12 Conclusions

The breadth of MCS options provides clinicians the opportunity to tailor therapy and management strategies to a patient's clinical status and unique needs. Understanding advantages and limitations of various devices, combined with algorithms, such as an approach based on INTERMACS status, may assist in optimizing decision-making. Future developments in assist device technology portend exciting frontiers for advanced HF support.

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Part III

ECMO for Respiratory Support

Ventilatory Management of ARDS Before and During ECMO

20

Giacomo Bellani, Giacomo Grasselli, and Antonio Pesenti

20.1 What Is Acute Respiratory Distress Syndrome (ARDS)?

20.1.1 Definition

The first report of adult respiratory distress syndrome (ARDS, the term “adult” was later replaced with “acute” acknowledging that the syndrome could also occur in children) was published by Ashbaugh and coworkers in 1967 [1]. ARDS is characterized by an acute onset of respiratory failure with arterial hypoxemia and lung stiffening, not arising from cardiac failure, but rather due to a massive “lesional” (i.e., caused by an increased permeability of the alveolar-capillary membrane) pulmonary edema. While the main features of the syndrome are well recognized, its formal definition remains more elusive. In 1994 the American/European consensus conference gave the first definition of ARDS [2], which was updated almost 30 years later by the “ARDS Definition Task Force” with the so-called Berlin definition [3], which is reported in Table 20.1.

20.1.2 Pathophysiology

ARDS can be seen as the result of a stereotyped response of the lungs to one or more inflammatory stimuli, originating primarily from the lungs (e.g., pneumonia) or from another organ (e.g., sepsis). The inflammatory response causes the recruitment of

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Table 20.1 “Berlin definition” of ARDS

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging ^a	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor is present
Oxygenation	
Mild	$200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$ ^b
Moderate	$100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$ ^b
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$

^aChest radiograph or computed tomography scan

^bThis may be delivered noninvasively in the mild acute respiratory distress group

neutrophils and macrophages, which extravasate from the capillaries to the alveoli, releasing inflammatory mediators and thereby further amplifying the inflammatory reaction [4]. This causes an increased permeability of the alveolar-capillary membrane, with the formation of a protein-rich alveolar edema which dramatically increases lung weight and stiffness [5]. The clinical consequence is the development of severe arterial hypoxemia and of a dramatic increase in the work of breathing, frequently requiring patient's intubation and the use of mechanical ventilation.

In the mid-1980s, computed tomography studies demonstrated that the lungs of ARDS patients were profoundly inhomogeneous, with areas of complete aeration loss, mostly located in the dorsal regions, and other zones of reduced or normal aeration. These observations led to the fundamental concept of “baby lung” [6]: the increased stiffness of ARDS lungs is mainly due to the low pulmonary volume available for tidal ventilation. Moreover, it was shown that the “baby lung” is a functional rather than an anatomical concept, and that a variable fraction of lung tissue can be regained to ventilation if an appropriate pressure is applied to the airways. In parallel with this findings, it was unveiled that mechanical ventilation per se could exacerbate the lung damage by means of the so-called ventilator-induced lung injury (VILI) [7], which is caused by two main pathogenetic mechanisms. First, the small “baby lung” is exposed to the risk of an exaggerated distension from tidal ventilation (overinflation), which is associated with excessive alveolar stretching. Second, the unstable alveoli, collapsed at end expiration, can be reopened during tidal insufflation: the cyclic alveolar opening and closing enhances the inflammatory response and further amplifies the lung damage.

20.2 How to Manage ARDS Before ECMO?

20.2.1 Ventilatory Strategies

The growing body of evidence regarding the aforementioned mechanisms of VILI stimulated the research of ventilatory strategies aimed at decreasing the stretch of

“ventilated” tissue and at promoting recruitment and ventilation of atelectatic lung, while minimizing the amount of cyclic intra-tidal recruitment/derecruitment.

20.2.1.1 Tidal Volume (Vt)

Tidal volume (Vt) is the amount of gas that is periodically insufflated in the lungs, and it is thus a major determinant of the cyclic distension of aerated parenchyma and of the possible genesis of intra-tidal recruitment/derecruitment: for this reason the use of “low” Vt is a cornerstone of ARDS treatment. A large study conducted by the National Institute of Health (USA) on 861 ARDS patients demonstrated a significant reduction of mortality when Vt was reduced from 12 to 6 ml/kg of ideal body weight [for men, $50\text{ kg} + 2.3\text{ kg} * (0.39 * \text{height (cm)} - 60)$; for women, $45.5\text{ kg} + 2.3\text{ kg} * (0.39 * \text{height (cm)} - 60)$], and plateau airway pressure (Pplat) was kept below 30 cmH₂O [8]. Since the publication of this study, it is recommended in all patients with ARDS to use a Vt of 6 ml/kg and to further reduce Vt or PEEP, if necessary, to keep Pplat below 30 cmH₂O. Interestingly, the beneficial effects of using low Vt are evident even if plateau pressures are not high [9]. Although this approach might appear simplistic (Does one size fits all?) and other investigators suggested that other parameters such as end-expiratory lung volume and transpulmonary pressure should be taken into account, it is important to underline that the reduction of Vt is still the (almost) only univocally accepted beneficial strategy in ARDS.

20.2.1.2 Respiratory Rate

An inevitable consequence of the reduction of Vt is the need to increase respiratory rate to values often considered “high,” way above 20 breaths per minute: for example, in the seminal “ARDSnet study,” the average respiratory rate was 29 ± 7 breaths per minute [8]. The need of elevated respiratory rates is further exacerbated by the increased alveolar dead space characteristic of ARDS, which translates in a very high ventilatory demand. The respiratory rate should be adjusted targeting a physiologic pH range (say between 7.3 and 7.45), rather than toward normal PaCO₂ values: unless contraindicated for intracranial problems, hypercapnia should be expected and tolerated (“permissive hypercapnia” [10]).

20.2.1.3 Setting of Positive End-Expiratory Pressure (PEEP)

Along with Vt, PEEP is probably the most relevant ventilatory parameter. The beneficial effect of PEEP derives mainly from the avoidance of alveolar derecruitment at end expiration, with consequent improvement in oxygenation. At the same time, PEEP expands also the aerated alveoli, with the risk of overdistension and VILI [11]. The “right” PEEP for each patient should ideally represent a balance between these two opposite phenomena. Recruitment and overdistension, however, cannot be measured routinely at the bedside but only inferred from indirect measures such as oxygenation and compliance. For these reasons how to set PEEP in ARDS patients remains a matter of debate. A widely diffuse approach is based on the use of “tables” reporting pairs of PEEP and FiO₂, which are raised (or decreased) in

parallel to reach a given oxygenation target [12]. Other authors proposed to set PEEP as high as possible to achieve a P_{plat} of 30 cmH₂O with a V_t of 6 ml/kg [13]. Other more “physiological” approaches select PEEP levels by simultaneously taking into account the effect of PEEP on compliance and gas exchange, particularly aiming to identify the PEEP level associated with the best compliance [14]. However, independently of the approach used, there is quite strong evidence in the literature suggesting that higher PEEP levels are beneficial in the most severe subcategory of ARDS patients [15].

Finally, since low V_t and high respiratory rate ventilatory strategies can easily lead to the development of intrinsic PEEP [16], this parameter should be periodically measured by end-expiratory holds.

20.2.1.4 Recruitment Maneuvers

It is well known that the inspiratory pressure required to reopen derecruited alveoli is by far higher than that necessary to keep the same alveoli open. On this concept relies the rationale of recruitment maneuvers, in which airway pressure is transiently increased to levels much higher than those achieved during regular tidal ventilation, typically equal or above 40 cmH₂O. The most common effect observed is an improvement of arterial oxygenation, which usually indicates that alveolar recruitment has occurred. If the oxygenation improvement is only transient and vanishing, this likely indicates that the set PEEP level is not adequate to avoid derecruitment of the recruited alveoli, prompting the need for a new recruitment maneuver followed by an increase in PEEP [17]. Several types of recruitment maneuvers have been described in the literature, including the “40-by-40” (airway pressure held for 40” at 40 cmH₂O) and periodic SIGHs [18]. Recruitment maneuvers tend to be more efficacious during the early course of the disease [19]. A meta-analysis showed that recruitment maneuvers are safe and that the most common side effect is a transient and self-resolving hypotension [20]; at the same time, it is unknown if a systematic use of recruitment maneuvers has any impact on patient’s outcome.

20.2.1.5 High-Frequency Oscillatory Ventilation (HFOV)

HFOV is a ventilatory technique, widely applied in the neonatal population, in which very small tidal volumes (1–2 ml/kg) are delivered at very high respiratory rates (5–10 breaths per seconds), while mean airway pressure is kept at levels much higher than those achieved during conventional mechanical ventilation to promote alveolar recruitment. By these mechanisms, HFOV is known to improve oxygenation, and for this reason, it is often regarded as a “rescue treatment” in refractory hypoxicemic ARDS. Following some preliminary encouraging data suggesting a potential benefit from the systematic application of HFOV in ARDS patients, two large multicenter randomized trials [21, 22] were conducted to compare HFOV with a conventional “lung protective” strategy in patients with moderate/severe ARDS: both failed to demonstrate any survival benefit of HFOV and quite surprisingly a mortality reduction was not observed even in the subgroup of more severely hypoxicemic patients.

20.2.1.6 The Role of Spontaneous Breathing

Spontaneous assisted ventilatory modalities (aimed at maintaining a variable amount of diaphragmatic activity supported by the mechanical ventilator) are widely employed during weaning from mechanical ventilation, but the preservation of spontaneous breathing also during the “acute phase” of ARDS bears some advantages, including improved ventilation-perfusion matching, alveolar recruitment, decreased sedation needs, lower hemodynamic impact, and reduced diaphragmatic dysfunction [23]. A large recent randomized controlled trial, however, showed a significant benefit on mortality when patients with more severe forms of ARDS (with a $\text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg}$) received neuromuscular blockade with cisatracurium during the first 48 h of ventilation, while neuromuscular paralysis was promptly ceased after this period [24]. The implications of this work should be carefully considered: the paper does not show that spontaneous breathing should be completely avoided during ARDS, but it underlines that neuromuscular blockade should be thoughtfully considered in the early phases of most severe disease since the pressure generated by spontaneously breathing patients can be very high with potentially injurious consequences.

20.2.2 Non-ventilatory Strategies

20.2.2.1 Pharmacologic Strategies

In recent years several pharmacological strategies aimed at modifying the clinical course of ARDS have been proposed and tested in the clinical field [25], including (only to quote some) pulmonary surfactant, activated protein C, salbutamol, omega-3 fatty acids, and caloric restriction. Unfortunately none of these drugs seems to have any beneficial effect on patient survival, and in some cases, a higher incidence of serious adverse events has been observed. Thus, to date, no drug is currently approved for specific ARDS treatment. Nitric oxide is a powerful pulmonary vasodilator: for this reason, when given by inhalation, it provides selective vasodilation of ventilated lung regions, thus improving gas exchange in the majority of ARDS patients, but again without a positive effect on survival [26]. However, given its powerful, but transient, effect on oxygenation, inhaled nitric oxide remains a useful rescue tool for refractory hypoxemia.

20.2.2.2 Prone Position

The use of prone position has been proposed in the 1980s as a tool to improve oxygenation: indeed when ARDS patients are turned prone, arterial oxygenation improves in about 60–70 % of the cases [27]. Different mechanisms are involved: more homogeneous distribution of ventilation, recruitment of dorsal lung segments, and improved ventilation-perfusion matching [28]. This may ultimately lead to an optimal recruitment at a given level of PEEP with a reduced risk of VILI [29]. As opposed to other rescue therapies, the effect of prone position on mortality is becoming more clear. A recent meta-analysis [30] of confirmed the beneficial effect of prone position on oxygenation and revealed a survival benefit in the population of

more severely hypoxic patients (those having a $\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$). Moreover, an elegant randomized controlled trial was recently published: severe ARDS patients ($\text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg}$ after 12–24 h of MV) were randomized to standard treatment in supine position or to undergo prone position session lasting 16 h, which were interrupted if oxygenation worsened (as compared to supine position) in two consecutive sessions. By this approach the authors were able to demonstrate a reduction of both 28- and 90-day mortality (from 33 to 16 % and from 41 to 24 %, respectively) [31], suggesting that prone position is likely to decrease mortality if applied early, in severe ARDS patients and interrupted if no response is seen.

20.3 How to Manage ARDS During Extracorporeal Membrane Oxygenation (ECMO)?

The classical indications for ECMO in ARDS patients are as follows: a) refractory impairment of gas exchanges despite an optimized ventilatory strategy (i.e., use of protective mechanical ventilation with low V_t and high PEEP and no response to less invasive rescue therapies) and b) the need to apply unacceptably high V_t and/or inspiratory pressures to support oxygenation. An additional indication is represented by interhospital transportation of unstable patients [27].

However, the optimal setting of the mechanical ventilator during ECMO is still a matter of debate, and no specific studies have been conducted to address this issue.

20.3.1 Controlled Mechanical Ventilation During ECMO

With few exceptions, in the first days after ECMO connection, patients are heavily sedated, if necessary paralyzed and kept on controlled mechanical ventilation.

The main goal of ECMO is to support gas exchanges while minimizing the risk of VILI. ECMO is an extremely efficient tool for CO_2 removal, and its efficiency increases with increasing pCO_2 values of the blood entering the artificial lung: for this reason, at the moment of ECMO institution, great caution must be exerted to avoid excessive shifts in blood pCO_2 and pH. To do this, a very slow increase of the sweep gas flow is coupled with a parallel reduction of the minute ventilation of the native lung.

The latter is usually obtained through a reduction of both tidal volume and respiratory rate, which in most cases translates into a reduction of more than 50 % of the pre-ECMO minute ventilation [32]. Most centers suggest to decrease respiratory rate to 10–15 breaths/min and to increase the inspiratory time. All the experts agree on the importance of keeping “lung rest” settings, by limiting plateau inspiratory pressure to minimize the risk of barotrauma. The guidelines of the Extracorporeal Life Support Organization (ELSO) recommend a Pplat limit of $\leq 25 \text{ cmH}_2\text{O}$ [33]; the same target was adopted in the largest randomized trial on ECMO published to date (the CESAR trial) [34], while in other case series, the Pplat limit was fixed at $30 \text{ cmH}_2\text{O}$.

A recent study on the cohort of patients treated with ECMO for H1N1-associated ARDS in French ICUs (the national REVA registry) showed that after ECMO connection, the mean V_t was reduced from 6.7 to 3.9 ml/kg and the mean P_{plat} from 32 to 26 cmH₂O. Interestingly, the authors of the study concluded that “under ECMO an ultraprotective ventilation strategy minimizing P_{plat} may be required to improve outcome” [35]. Based on these observations, some clinical trials adopting an “ultraprotective” P_{plat} target of 20 cmH₂O have been designed.

An open issue is how to set PEEP once the patient is connected to ECMO. In the CESAR trial, PEEP was abruptly reduced to 10–15 cmH₂O [34]; by contrast, other experts suggest to keep PEEP unchanged or even to increase it, with the aim of avoiding a sudden reduction of mean airway pressure that could lead to lung collapse and pulmonary flooding.

Indeed an important dilemma in these patients is as follows: Should we let the lungs collapse or should we try to keep them open? Supporters of the “open lung approach” claim that recruited (ventilated) lungs have a lower risk of superinfection, better surfactant function, and better secretion clearance [36]. If this is true, it remains unclear how to recruit the lungs while keeping protective ventilatory settings. An option may be the periodic application of recruitment maneuvers, but no data on their safety and efficacy in ECMO patients are available. Some referral centers (e.g., the University of Michigan) routinely use prone position during ECMO to improve the ventilation-perfusion matching [37], and some reports in the literature have shown that proning patients while on ECMO is feasible and safe [38, 39]. It must be underlined, however, that prone positioning during ECMO may be associated with potentially dramatic complications, such as compression or inadvertent removal of vascular cannulas: for this reason, it should be performed only in centers with extensive experience in the field [40].

Finally, after ECMO institution it is recommended to reduce the ventilator FiO_2 to the lowest level compatible with a target arterial pO_2 of about 55–60 mmHg, to reduce oxygen toxicity and the risk of resorption atelectasis [33]. Some authors recommend to abruptly reduce the ventilator FiO_2 to very low levels: in the CESAR trial, for example, FiO_2 was set to 30 % [34]. However, it must be remembered that if the patient is severely hypoxic and intrapulmonary shunt is lower than 100 % (which means that the native lung still contributes to arterial oxygenation), such a marked decrease of the ventilator FiO_2 may lead to a significant worsening of oxygenation that could be compensated only with the use of extremely high extracorporeal blood flows.

20.3.2 Assisted Spontaneous Breathing During ECMO

When the native lung function and the patient’s clinical conditions improve, a shift from controlled mechanical ventilation to an assisted spontaneous breathing mode can be considered. The potential advantages of the preservation of a spontaneous breathing activity in ARDS patients have already been described in a previous paragraph. During ECMO, there is a complex interplay between the patient’s own

respiratory drive, the level of sedation and the ventilation of the artificial lung: by varying the level of sedation and the sweep gas flow, we can change the relative fraction of total CO₂ production which is removed by the native and the artificial lung. In other words, modulating the level of extracorporeal assist may facilitate the switch to an assisted modality of ventilation by controlling the patient's respiratory drive.

The most commonly used mode of assisted ventilation is pressure-support ventilation (PSV), but recent data seem to indicate that, at least in certain subgroups of patients, the use of neurally adjusted ventilatory assist (NAVA) may have some additional benefits.

A detailed description of NAVA is beyond the scope of this paragraph: briefly, during NAVA the ventilator inspiratory assist is delivered in synchrony and in proportion to the diaphragm electromyogram (EAdi), which is acquired through a specialized nasogastric tube [41].

Literature data on the use of NAVA during ECMO are limited. Karagiannidis et al. studied the effect of different sweep gas flows on gas exchange and ventilation in a small sample of six patients: after gas flow reduction, the patients rapidly increased their minute ventilation to restore a physiological pH value but tended to maintain a "protective" Vt. The authors concluded that "the combination of NAVA and ECMO may permit a closed-loop ventilation with automated protected ventilation" [42].

More recently, Mauri et al. compared PSV and NAVA in 10 patients undergoing ECMO for severe primary ARDS with very low respiratory system compliance: they observed a better patient-ventilator interaction and a reduction of asynchronies with NAVA [43], but further studies are needed to confirm these findings.

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21.1 Introduction

Extracorporeal membrane oxygenation is a highly effective technique for cardiopulmonary support, but it is not devoid of complications. Hence, proper monitoring is essential before, during, and after ECMO application. In this chapter, we will discuss respiratory monitoring during venovenous ECMO (VV ECMO), while the indications for ECMO institution and weaning from ECMO will be reviewed in specific chapters 16, 20, 26, 27, 40. Respiratory monitoring during venoarterial ECMO is elucidated in Chap. 33.

ECMO can totally or partially substitute the gas exchange functions of patient lungs: therefore, during VV ECMO, the interpretation of parameters usually employed to monitor respiratory function, such as arterial partial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2), must take into account the contribution of extracorporeal gas exchange. Also other parameters, such as intrapulmonary shunt fraction (natural lung shunt, Q_s/Q_t), may be significantly affected by extracorporeal gas exchange. Moreover, VV ECMO substantially affects mixed venous blood gas composition, increasing oxygen and reducing carbon dioxide content, and may

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Table 21.1 Facsimile of the electronic spreadsheet used at the San Gerardo Hospital, Monza, Italy, to monitor patients on VV ECMO; the blue boxes show parameters and measures performed with the clinical FiO_2 , while orange boxes require FiO_2 100 % in order to calculate the “true” shunt. We report all the formulas used to compute each parameter

Name		SHUNT (100% NL FiO_2 and 100% GF FiO_2)	SHUNT Blood Gases (100% NL FiO_2 and 100% GF FiO_2)
Data			ARTERIAL Blood Gas
ICU Day n°		Theoretical Alveolar O ₂ Pressure (NL FiO_2 = 100) $\text{PAO}_2 = (\text{NL } \text{FiO}_2 \times 713/100) - (\text{PartCO}_2/0,8)$	mmHg
ECMO Day n°		Theoretical Pulmonary Capillary Hb Saturation $\text{pCO}_2\text{Hb} = 100 - \text{averageCOHb} - \text{averageMetHb}$	%
ECMO Circuit n°		Theoretical Pulmonary Capillary O ₂ Content $\text{Cco}_2 = 0,0031 \times \text{PAO}_2 + 1,34 \times \text{pCO}_2\text{Hb} \times \text{avHb}$	ml/dl
ECMO Circuit Day n°		Venous O ₂ Content $\text{CvO}_2 = 0,0031 \times \text{PvO}_2 + 1,34 \times \text{vO}_2\text{Hb} \times \text{avHb}$	ml/dl
HEMODYNAMIC			MIXED VENOUS Blood Gas
Cardiac Output (CO)	Liters/min	Arterial O ₂ Content $\text{CaO}_2 = 0,0031 \times \text{PartO}_2 + 1,34 \times \text{artO}_2\text{Hb} \times \text{avHb}$	ml/dl
Body Temperature	celcius ¹	ML O ₂ Pressure (GF FiO_2 = 100) $\text{PMLO}_2 = (\text{GF } \text{FiO}_2 \times 713/100) - (\text{PinCO}_2/0,8)$	mmHg
Heart Rate (HR)	beats/min	Theoretical ML Capillary Hb Saturation $\text{pCO}_2\text{Hb} = 100 - \text{averageCOHb} - \text{averageMetHb}$	%
Systolic Art Pressure (sPA)	mmHg	Theoretical ML Capillary O ₂ Content $\text{CcmLO}_2 = 0,0031 \times \text{PMLO}_2 + 1,34 \times \text{MLO}_2\text{Hb} \times \text{avHb}$	ml/dl
Diastolic Art Pressure(dPA)	mmHg	ML Inlet O ₂ Content $\text{CinO}_2 = 0,0031 \times \text{PinO}_2 + 1,34 \times \text{inO}_2\text{Hb} \times \text{avHb}$	ml/dl
Mean Art Pressure (mPA)	mmHg	ML Outlet O ₂ Content $\text{CoutO}_2 = 0,0031 \times \text{PoutO}_2 + 1,34 \times \text{outO}_2\text{Hb} \times \text{avHb}$	ml/dl
Central Venous Pressure (CVP)	mmHg	Shunt NL (Q _{sh} /Q _{nl}) = 100 x (Cco ₂ - CaO ₂)/(CcmLO ₂ - CvO ₂)	%
Sistolic Pulmonary Artery Pressure (sPAP)	mmHg	Shunt ML = 100 x (CcmLO ₂ - CoutO ₂)/(CcmLO ₂ - CinO ₂)	%
Diastolic Pulmonary Artery Pressure (dPAP)	mmHg	Pulmonary Wedge Pressure (WP) $\text{V'CO}_2 - R/BF = (100\% \text{ NL } \text{FiO}_2 \text{ and } 100\% \text{ GF } \text{FiO}_2)$	mmHg
Mean Pulmonary Artery Pressure (mPAP)	mmHg	Cardiac Output 100% NL FiO_2 and 100% GF FiO_2 $\text{CO}_{nl} = (\text{CaO}_2 - \text{CvO}_2) \times \text{CO} \times 10$	Liters/min
Pulmonary Vascular Resistance (PVR) (mPAP - WP)/80/CO	dyne x sec x cm ⁵	$\text{V'CO}_{nl} = (\text{CaO}_2 - \text{CvO}_2) \times \text{CO} \times 10$	ml/min
Pulmonary Vascular Resistance (mPAP - WP)/80/CO	dyne x sec x cm ⁵	$\text{V'CO}_{ml} = (\text{CoutO}_2 - \text{CinO}_2) \times \text{BF} \times 10$	ml/min
Continuous Mixed Venous Oxygen Saturation (SvO ₂)	%	$\text{V'CO}_{tot} = \text{V'CO}_{nl} + \text{V'CO}_{ml}$	ml/min
VENTILATION - NATURAL LUNG (NL)		Theoretical Venous O ₂ Content $\text{CtvO}_2 = \text{CaO}_2 - [\text{V'CO}_{tot}/(\text{CO} \times 10)]$	ml/dl
Tidal Volume (TV)	ml	ECMO Recirculation Fraction $R/BF = 100 \times (\text{CinO}_2 - \text{CtvO}_2)/(\text{CoutO}_2 - \text{CtvO}_2)$	%
Total Minute Volume (MV)	Liters/min	ECMO - MEMBRANE LUNG (ML)	ECMO OUTLET Blood Gas
Respiratory Rate	breaths/min	ECMO Blood Flow (BF)	pHout
Inspiratory Time	seconds	ECMO Centrifugal Pump rpm	rpm/min
Clinical NL FiO_2	%	ML Temperature	celcius ¹
Positive end expiratory pressure (PEEP)	cmH ₂ O	ML Gas Flow (GF)	l/min
PEEP (autoPEEP)	cmH ₂ O	Blood Pressure PreML (PpreML)	mmHg
Peak Pressure (P_{peak})	cmH ₂ O	Blood Pressure PostML (PpostML)	mmHg
Plateau Pressure (P_{plat})	cmH ₂ O	ML Resistance = [PpreML - PpostML]/BF	mmHg/l/min
Mean Airway Pressure(PAW)	cmH ₂ O	$V'CO_2 - \text{Dead Space}$	Base Excess (outBE)
Respiratory System Compliance (Cpl_{rl})	ml/cmH ₂ O	Mean Expiratory CO ₂ Pressure (eCO ₂)	mmHg
VENTILATION - NL (OPTIONAL)		Mean Expiratory CO ₂ Pressure (eCO ₂) _{NL} = ($e\text{CO}_2\text{ML} \times \text{CO} \times 1000 / 760$)	AVERAGE OF 4 Blood Gas
SIGH Pressure	cmH ₂ O	$V'CO_2 = \text{V'CO}_{nl} + \text{V'CO}_{ml}$	ml/min
SIGH Volume	ml	Natural Lung Dead Space Fraction	%
Spontaneous Minute Volume (NAVA) Eadi peak	microVolt	$D_{Sigh} = 100 \times (\text{PaCO}_2 - e\text{CO}_2\text{NL})/\text{PaCO}_2$	pHa
End Expiratory Lung Volume (EELV-FRC)	ml	$e\text{CO}_2\text{NL} = 100 \times (\text{PoutCO}_2 - e\text{CO}_2\text{ML})/\text{PoutCO}_2$	PaO ₂
End inspiratory Esophageal Pressure (P_{ei})	cmH ₂ O	$\text{PaO}_2/\text{FiO}_2 - \text{O}_2 - \text{Oxygen Delivery}$	mmHg
Endinspiratory Transpulmonary Pressure (P_{pe})	cmH ₂ O	$\text{O}_2/\text{FiO}_2 \times \text{PAW} / \text{PaO}_2$	aCOHb
		$\text{cmH}_2\text{O/mmHg}$	aMetHb
		Base Excess (aBE)	meq/l
		ahCO_2	mmol/L
		Lactic Acid	mmol/L
		Clinical ARTERIAL Blood Gas (Clinical FiO_2 , NL and Gas Flow FiO_2)	

itself affect lung function, for example, altering the hypoxic vasoconstriction. Also respiratory mechanics (respiratory system compliance, airway resistance, lung volume) and ventilatory parameters (mean airways pressure, plateau pressure, trans-pulmonary pressure) need to be closely monitored, to assess the severity of lung disease and prevent ventilator-induced lung injury (VILI).

To date very little data exist on respiratory monitoring during ECMO support, therefore we will start from available data in patients with ARDS, and, subsequently, we will discuss the topic during VV ECMO with a physiological approach supported by data from literature and the experience of our institution. Table 21.1 shows a facsimile of the electronic spreadsheet used in our institution to monitor patients on VV ECMO. Our daily evaluation of patients on VV ECMO is performed with four blood gas analyses (arterial, mixed venous, ECMO inlet, and ECMO outlet) and

assessment of hemodynamic, ventilatory, and ECMO parameters. To understand the respiratory function of the natural lung (NL), we need to evaluate the role of VV ECMO and the hemodynamic status. If no major contraindications are present, all patients treated with VV ECMO are monitored with a Swan–Ganz catheter with continuous measurement of mixed venous oxygen saturation (SvO_2). The pulmonary artery catheter not only allows the measurement of pulmonary arterial pressure and cardiac output but also allows a precise assessment of the mixed venous oxygen content; moreover, it provides continuous monitoring of core temperature which is essential during ECMO institution or ECMO circuit replacement. From the recorded data, we can calculate the oxygen added to the blood by the NL ($V'O_2$ NL) and by the membrane lung (ML) ($V'O_2$ ML), the carbon dioxide removed by the NL ($V'CO_2$ NL) and by the ML ($V'CO_2$ ML), and the intrapulmonary shunt fraction (shunt NL); it is also possible to estimate the extracorporeal blood flow recirculation fraction (R/BF) and other useful parameters to monitor the ML function as reported in Chap. 35.

Since the measurement of intrapulmonary shunt requires ventilation with pure oxygen, we usually perform this global daily assessment, setting the ventilator and sweep gas FiO_2 to 100 %. On the contrary, during the day, we prefer to assess arterial gases at the clinical FiO_2 and to continuously monitor the SvO_2 .

All these parameters are critical to understand and monitor the contribution of patient lungs to oxygenation and CO_2 removal: we will discuss these two functions separately, since they have different underlying physiological mechanisms, as suggested by Kolobow and Gattinoni in the late 1970s [1, 2].

21.2 Oxygenation

Hypoxemia, deficiency of oxygen in arterial blood, is a hallmark of ARDS; quantification of the degree of hypoxemia is critical to assess the severity of the disease and prevent tissue hypoxia. It is difficult to define hypoxemia based on a single PaO_2 threshold value. However, when PaO_2 is above 60 mmHg, the hemoglobin dissociation curve is almost flat, arterial hemoglobin oxygen saturation (aO_2Hb) is higher than 90 %, and the oxygen content of arterial blood is close to the maximum for a given hemoglobin content. Otherwise, PaO_2 levels below 40 mmHg, corresponding to an aO_2Hb lower than 75 %, invariably result in tissue hypoxia [3]. Hence, several authors [4, 5] suggest a target PaO_2 value between 50 and 60 mmHg or a target aO_2Hb between 85 and 95 %.

Since in ARDS patients severe hypoxemia is mainly caused by intrapulmonary shunt (see below), VV ECMO, increasing mixed venous oxygen content, may efficiently improve arterial oxygenation if the extracorporeal blood flow is adequate. If the native lung function is completely compromised (i.e., if the intrapulmonary shunt fraction approaches 100 %), an extracorporeal blood flow higher than 4–4.5 l/min (in the absence of extracorporeal blood flow recirculation) will be required to support oxygenation: in such scenario, the arterial oxygen content would be close to the mixed venous one, since NL does not contribute to gas exchange, and therefore oxygenation is completely dependent on ML function (see Fig. 21.1). When the native lung function improves, the difference between arterial and mixed venous oxygen content increases, which further stresses the importance of continuously monitoring mixed venous blood.

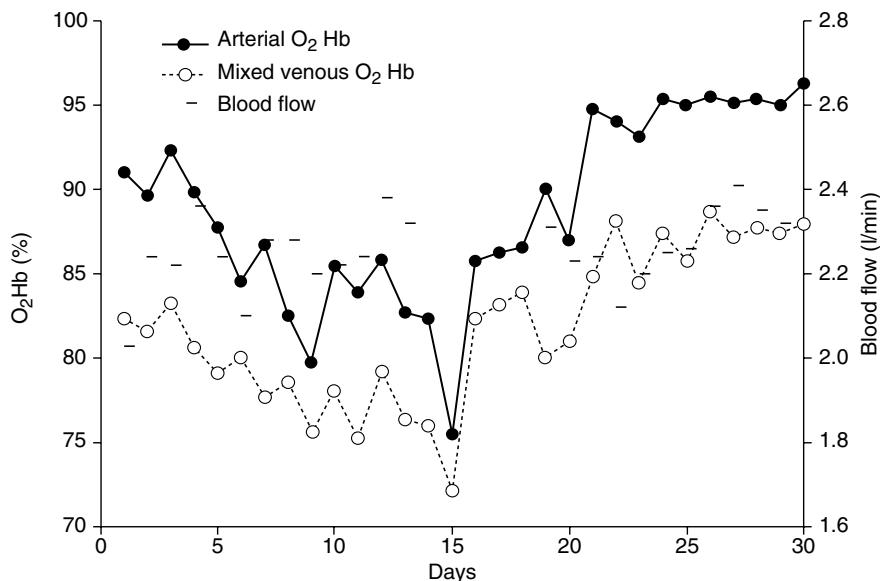


Fig. 21.1 Arterial and mixed venous O₂Hb saturation during days in a patient successfully treated with VV ECMO. After approximately 18 days, the patient improved, and, despite a reduction in extracorporeal blood flow, both arterial and mixed venous O₂Hb saturation ameliorated

21.2.1 PaO₂ and PaO₂/FiO₂

A variety of indices have been introduced to evaluate oxygenation: the PaO₂/FiO₂ ratio, the difference between alveolar and arterial PO₂, the intrapulmonary shunt fraction, and the oxygenation index. Since the definition of ARDS proposed in 1994 by the American-European Consensus Conference (AECC) [6], PaO₂/FiO₂ ratio is the more commonly employed index and has been used to differentiate patients with acute lung injury (ALI) (PaO₂/FiO₂ < 300 mmHg) from those with acute respiratory distress syndrome (ARDS) (PaO₂/FiO₂ < 200 mmHg). The PaO₂/FiO₂ ratio also appears in the new ARDS definition (proposed in 2011 as the “Berlin” definition), where it is used to define three categories of respiratory insufficiency: mild (200 mmHg < PaO₂/FiO₂ ≤ 300 mmHg), moderate (100 mmHg < PaO₂/FiO₂ ≤ 200 mmHg), and severe (PaO₂/FiO₂ ≤ 100 mmHg) [7]. Such degrees of severity were associated with different mortality and duration of mechanical ventilation, although the prognostic role of PaO₂/FiO₂ ratio in ARDS patients remains to be investigated since previous publications did not show any association between severity of hypoxemia and patient outcome [8, 9]. Such conflicting results can be explained by the fact that the PaO₂/FiO₂ ratio is strongly influenced by the FiO₂ at which it is measured. In patients with moderate (<30 %) intrapulmonary shunt, the PaO₂ is greatly affected by FiO₂ and their relationship appears to be nonlinear: in particular, the PaO₂/FiO₂ ratio is greater at both the extremities of the FiO₂ range

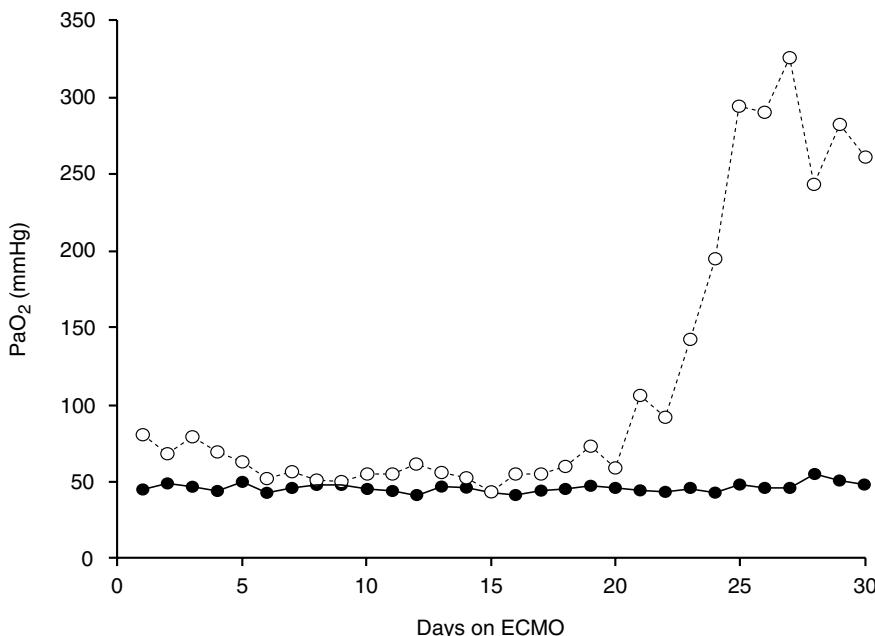


Fig. 21.2 PaO_2 over time of two patients on VV ECMO for severe respiratory failure, FiO_2 100 %. *Open circles*: the patient was successfully disconnected from the ECMO. *Solid circles*: the patient did not survive, his intrapulmonary shunt was always above 95 %, and the PaO_2 was always lower than 50 mmHg in spite of an extracorporeal BF always higher than 3 l/min

compared to intermediate FiO_2 values [10, 11]. Important variations of FiO_2 may therefore significantly alter the $\text{PaO}_2/\text{FiO}_2$ ratio, leading to different classifications of the disease [12]. On the other hand, in patients with intrapulmonary shunt higher than 30 %, who may require VV ECMO support, PaO_2 is relatively independent from FiO_2 and may be a good indicator of lung function; however, also the $\text{PaO}_2/\text{FiO}_2$ ratio appears almost constant, since the commonly employed FiO_2 is generally elevated. The average $\text{PaO}_2/\text{FiO}_2$ ratio at enrolment in the “CESAR” ECMO trial was 76 mmHg [13], just slightly higher than that reported by the Italian ECMO network (ECMONet) in 153 critically ill patients before ECMO institution (63 mmHg) [14].

When the patient has a considerable intrapulmonary shunt and remains hypoxic even during VV ECMO, PaO_2 itself is a good indicator of the native lung condition. Figure 21.2 depicts the variation of PaO_2 in two patients undergoing VV ECMO, recorded during the daily assessment with FiO_2 100 %. In one patient (solid circles), PaO_2 remained always below 50 mmHg despite the maximization of the extracorporeal support (blood flow ranged between 3 and 3.5 l/min), because the intrapulmonary shunt was almost 100 %; the second patient (open circles) showed a significant PaO_2 improvement which allowed disconnection from the bypass.

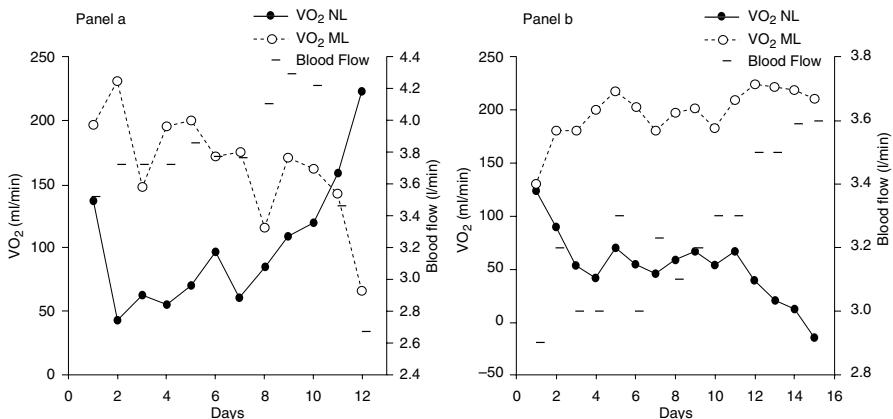


Fig. 21.3 Panel (a): $\dot{V}O_2$ ML and $\dot{V}O_2$ NL in a patient disconnected from the VV ECMO after 12 days. Panel (b): $\dot{V}O_2$ ML and $\dot{V}O_2$ NL in a patient who died during VV ECMO. Measuring the relative contribution of the NL and the ML allows to monitor the evolution of the native lung disease over time. In panel (b), $\dot{V}O_2$ NL eventually became negative, since NL shunt was 100 % and the lungs were extracting oxygen from the blood

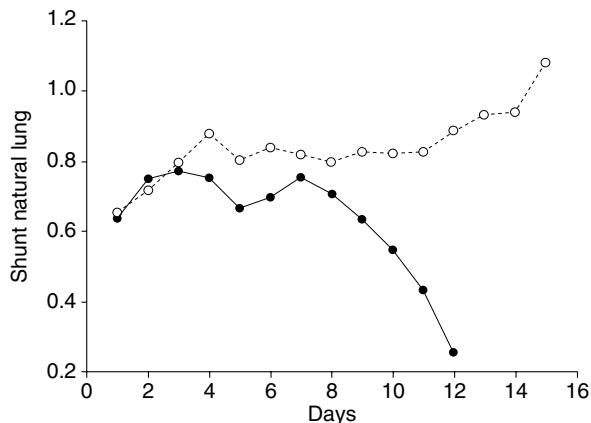
21.2.2 Oxygenation Index

Although PaO_2 and possibly also the PaO_2/FiO_2 seem good indicators of oxygenation, they do not take into account the cost in terms of positive pressures that must be applied by the ventilator. The oxygenation index (OI) overcomes this limitation, including the mean airway pressure (PAW) value in its calculation as shown in Table. 21.1 [15, 16]. The OI has gained widespread popularity in neonatal and pediatric ECMO patients, but it has recently been proposed also in adults: values above 30 are usually considered an indication for ECMO institution. For example, among the 60 critically ill patients admitted to the Italian ECMOnet ICUs and treated with ECMO support, the median OI ($cmH_2O/mmHg$) was 36.3 and 33.9, respectively, for patients with or without influenza A H1N1 [14].

21.2.3 Membrane Lung and Natural Lung Oxygen Supply

PaO_2 , PaO_2/FiO_2 ratio, and the OI do not take into account the oxygen supplied by the ECMO support: indeed, during VV ECMO arterial oxygenation depends on the oxygen added to the blood by the ML ($\dot{V}O_2$ ML) and by the NL ($\dot{V}O_2$ NL). At equilibrium, the sum of $\dot{V}O_2$ ML and $\dot{V}O_2$ NL equals the total body oxygen consumption. Figure 21.3 shows an example of trends of $\dot{V}O_2$ ML and $\dot{V}O_2$ NL in two patients. Panel a: an increase in $\dot{V}O_2$ NL was observed after 8 days and eventually allowed to reduce the extracorporeal support and successfully disconnect the patient from the ECMO. In panel b, $\dot{V}O_2$ NL showed a constant decline, and eventually after 15 days of ECMO, the lungs were actually extracting oxygen from the blood resulting in a negative $\dot{V}O_2$ NL.

Fig. 21.4 Intrapulmonary shunt of the same two patients reported in Fig. 21.3. Solid circles: the NL shunt starts to improve after 8 days of ECMO support, and the patient was successfully disconnected from the ECMO when NL shunt was lower than 30 %. Empty circles: the patient died during ECMO; after 12 days, the natural lung function worsened and eventually the shunt was 100 %



21.2.4 Intrapulmonary Shunt

Intrapulmonary shunt has been preferred by some authors [11, 17–19] to describe oxygenation in ARDS patients, even if its calculation requires the placement of a pulmonary arterial catheter for mixed venous blood sampling. Intrapulmonary shunt is described as the fraction of cardiac output perfusing nonventilated alveoli and therefore not participating to gas exchange. In healthy subjects, only a small fraction of the cardiac output is shunted, due to perfusion of bronchial tissue and a small amount of coronary venous blood. An intrapulmonary shunt fraction higher than 10 % of the cardiac output results in hypoxemia, since the non-shunted blood, due to the peculiar form of the oxyhemoglobin dissociation curve, is not able to load the extra amount of oxygen required to fully saturate the shunted blood. The nomenclature is not strictly defined, but usually the term “true shunt” is referred to the areas with zero ventilation/perfusion ratio and is calculated as showed in Table 21.1 while breathing pure oxygen. “Venous admixture” is obtained from the same equation while breathing an oxygen concentration lower than 100 % and embeds three components: ventilation/perfusion mismatch, diffusion limitation, and “true” shunt; for this reason, it is also referred as physiologic shunt. In our experience, ECMO support is deemed necessary in patients with an intrapulmonary shunt fraction exceeding 50–60 %, while disconnection is attempted when shunt becomes lower than 40 % (see Fig. 21.4). It is commonly believed that intrapulmonary shunt increases when FiO_2 or mixed venous oxygen tension (PvO_2) increases, which is exactly what ECMO does. However, a well-designed study on severe ARDS patients undergoing VV ECMO examined the specific role of PvO_2 and FiO_2 and showed that reducing PvO_2 by decreasing the FiO_2 of the ML caused a dramatic fall in PaO_2 , but the intrapulmonary shunt fraction did not substantially change; similarly, increasing the ventilator FiO_2 from 60 to 100 % did not modify the intrapulmonary shunt [20]. These results, partially in contrast with other literature data, may indicate that in those ARDS patients, the hypoxic vasoconstriction was blunted.

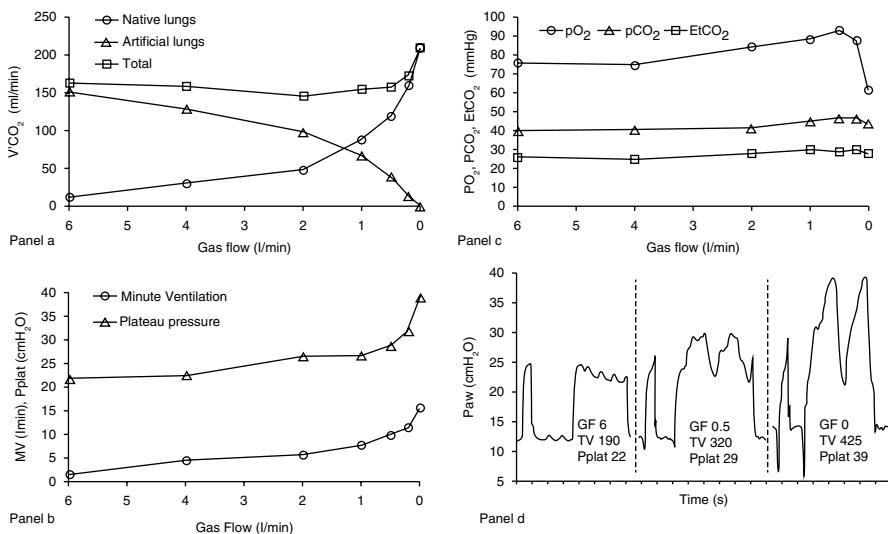


Fig. 21.5 Example of VV ECMO patient's global assessment. Relationship between native and extracorporeal $V'\text{CO}_2$ (panel a), plateau pressure, minute ventilation (panel b), arterial and exhaled gases (panel c) and airways pressure waveforms (panel d) during a progressive reduction of sweep gas flow of the membrane lung in a patient undergoing VV ECMO (BF 3.5 l/min) on spontaneous ventilation (mode: pressure support, support level 12 cmH₂O, PEEP 12 cmH₂O, FIO₂ 55 %). In panel d, GF and TV refer to the sweep gas flow (l/min) of artificial ML and to the tidal volume (ml) of NL, respectively

21.3 Carbon Dioxide

Also when analyzing arterial PCO_2 and pH, we need to consider the relative role of NL and ML. Extracorporeal CO_2 removal, differently from extracorporeal oxygenation, which mainly depends on extracorporeal blood flow, is primarily related to sweep gas flow: therefore, $V'\text{O}_2$ and $V'\text{CO}_2$ are independent and need to be measured separately. A decrease in sweep gas flow reduces the artificial lung CO_2 extraction (nonlinearly; see Fig. 21.5 panel a), and consequently if the ventilation of the natural lung is not adjusted, PaCO_2 will increase. In a spontaneously breathing patient, a reduction of the sweep gas flow will be associated with an increased respiratory drive, leading to an increase in minute ventilation and $V'\text{CO}_2$ of NL (Fig. 21.5, panels a and b). In the patient shown in Fig. 21.5, the progressive reduction of sweep gas flow from 6 to 0.5 l/min (and of $V'\text{CO}_2$ of ML from 150 to 40 ml/min) was associated with increased spontaneous patient's efforts, which may enhance lung recruitment and actually resulted in a higher PaO_2 (panel c). However, when the gas flow was further reduced, the patient's respiratory efforts became excessive, leading both to a dangerous elevation of plateau pressures (panels b and d) and to a not endurable increase of work of breathing and total CO_2 production (panel a). Furthermore, the higher respiratory muscles O₂ consumption and the concurrent reduction of the extracorporeal support caused a critical decrease in venous oxygen

saturation and ultimately a drop in PaO_2 (panel c). This example strongly supports the need for a global assessment of the patient, with simultaneous evaluation of gas exchanges (PaO_2 , PaCO_2) and of the ventilatory “load” imposed to the native lung (P_{plat} , minute ventilation). Monitoring the behavior to progressive re-loading of the native lung is helpful in indicating whether or not, and in the case how much, the patient is still dependent on the extracorporeal support (see Chap. 27 for further information on weaning from VV ECMO).

21.4 Respiratory Mechanics

The elastic characteristics of the respiratory system are described by the compliance of the respiratory system (Cpl_{RS} , ml/cmH₂O) which is the change in volume (ΔV) for any applied pressure variation (ΔP):

$$\text{Cpl}_{\text{RS}} = \frac{\Delta V(\text{ml})}{\Delta P(\text{cmH}_2\text{O})}$$

A normal value of Cpl_{RS} in healthy adults is around 100 mL/cmH₂O, but during invasive mechanical ventilation, the expected normal value is lower, around 50–60 mL/cmH₂O [21], and it further decreases down to 30–40 mL/cmH₂O or less in patients with ALI/ARDS [21, 22].

Some authors prefer to calculate the system elastance, which is the reciprocal of compliance and is therefore expressed as $\Delta P/\Delta V$.

The concept of “baby lung,” introduced by Gattinoni and Pesenti [23], states that the lungs in ARDS patients are not “stiff” per se, since the intrinsic elasticity of the aerated lung parenchyma appears nearly normal. Therefore, the reduction in Cpl_{RS} , always seen in patients with ARDS, is caused by the reduced dimension of the aerated lungs, the “baby lung.” Consequently, the Cpl_{RS} is linearly related to the lung volumes and reflects the degree of lung volume loss [22, 24, 25].

Although the Cpl_{RS} value was not included in the final version of the Berlin definition of ARDS, since it did not improve the patient outcome prediction, the panel of experts emphasized the importance of daily evaluation of Cpl_{RS} while managing ARDS patients [24]. The utility of Cpl_{RS} in patients on ECMO is even higher because it is not affected by the extracorporeal circulation and is an excellent indicator of the severity of the lung disease.

Generally, in adult patients, values of Cpl_{RS} above 30 ml/cmH₂O indicate clinical conditions that can be treated with conventional therapies, while values lower than 20–25 ml/cmH₂O are found in extremely severe medical conditions that often require extracorporeal support. Between these two extremes, there are a multitude of clinical situations that can be difficult to manage with conventional supports: the average Cpl_{RS} value of patients considered for ECMO treatment at the time of inclusion in the “CESAR” trial was 26 ml/cmH₂O [13]. Almost 30 years ago, Gattinoni demonstrated in a group of 36 patients with severe ARDS that Cpl_{RS} was the most useful measurement to guide the clinical management: all the patients, but one, with Cpl_{RS} below 25 needed ECMO support [24].

The measurement of Cpl_{RS} in intubated patient during mechanical ventilation is calculated with the following formula:

$$Cpl_{RS} = \frac{TV(\text{ml})}{P_{plat} - PEEP_{tot} (\text{cmH}_2\text{O})}$$

where TV is the tidal volume, P_{plat} is the airway pressure during an end-inspiratory pause of at least 3 s, and $PEEP_{tot}$ = set PEEP + auto-PEEP (or intrinsic PEEP). The $PEEP_{tot}$ is measured during an expiratory pause.

Until now we have considered the compliance of the respiratory system as a single entity, but it is well known that the respiratory system is constituted by two mechanical structures in series: the lung and the chest wall, therefore the applied pressure (ΔP) required to introduce an air volume (ΔV) in the system is spent in part to expand the lungs (transpulmonary pressure = airway pressure minus pleural pressure) and in part to expand the chest wall. The pleural pressure is clinically estimated by measuring the pressure inside the esophagus with a special nasogastric tube equipped with a balloon. In our institution the esophageal pressure is not routinely monitored, nevertheless some authors emphasize the critical role of transpulmonary pressure, also referred as lung stress, as the primary determinant of ventilator-induced lung injury [21]. Recently, G. Cortes and J.J. Marini suggested that monitoring transpulmonary pressure and functional residual capacity (FRC) at the bedside can improve the interpretation of conventional parameters of lung mechanics based on airway pressures alone and may help to “develop a ventilator strategy tailored to the specifics of a given patient” [26].

During the last influenza A (H1N1) pandemic, Grasso et al. applied these principles in a cohort of 14 patients with severe ARDS referred for extracorporeal membrane oxygenation [27]. In seven cases, the transpulmonary pressure was above 25 cmH₂O, and all these patients underwent ECMO. In the other seven cases, the transpulmonary pressure was lower than 25 cmH₂O and PEEP was raised (from 17.9 ± 1.2 to 22.3 ± 1.4 cmH₂O) to obtain a target transpulmonary pressure of 25 cmH₂O: this strategy improved oxygenation, allowing these patients to be successfully treated with conventional ventilation. In other words, the transpulmonary pressure measurement allows an estimation of the “real” driving pressure across the lung parenchyma, regardless of peculiar characteristics of the chest wall [26].

However, when the transpulmonary pressure is not available, clinicians may use its surrogate, the plateau pressure (P_{plat}) obtained with an inspiratory pause. In the year 2000, the ARDSnet seminal trial suggested not to exceed a P_{plat} of 30 cmH₂O in order to reduce VILI [28]. Recently two different studies, one performed by Bellani et al. with PET images [29] and the other by Terragni et al. with pulmonary computed tomography and pulmonary cytokines [30], suggested a lower safety limit for plateau pressure around 27 cmH₂O.

Also during spontaneous breathing, P_{plat} plays a critical role in the evaluation of patient effort and of the “safety” of native lung ventilation. Panel d in Fig. 21.5 shows inspiratory occlusions during pressure support ventilation at different extracorporeal supports. At high sweep gas flow, P_{plat} is 22 cmH₂O, 2 cmH₂O lower than the sum of PEEP (12 cmH₂O) plus pressure support (12 cmH₂O), indicating that

patient effort is negligible. At lower gas flows, the patient effort increases as demonstrated by the pressure waveform (deep deflections preceding the ventilatory trigger and during the end-inspiratory pause), and the P_{plat} value much greater than the sum of PEEP plus pressure support [31], clearly exceeding “safety” limits.

Another strategy frequently employed in our ICU to monitor patient effort and to detect patient–ventilator asynchronies, which are common in patients with extremely low Cpl_{RS} , is through the analysis of the diaphragm electrical activity (EA_{di}): this is obtained with a specific nasogastric tube and a mechanical ventilator employed to perform neurally adjusted ventilatory assist (NAVA). During pressure support ventilation, the EA_{di} signal may help to set the cycling criteria so as to improve patient–ventilator interaction or, when necessary, may allow to switch to the NAVA ventilatory mode, which supports the patient proportionally and in sync to the EA_{di} signal [32]. Furthermore, since EA_{di} is directly related to patient effort, its continuous recording may enable a real-time estimate of patient’s inspiratory effort through the assessment of a coefficient termed P_{musc}/EA_{di} index [33], which may be of extreme interest, especially during the weaning phase from ECMO.

The aerated lung volume in patients requiring VV ECMO can be particularly reduced, so VILI prevention strategies should be based on pressure limits rather than tidal volume indexed to the ideal body weight; alternatively, tidal volume may be indexed to the functional residual capacity (FRC), which is the volume of gas contained in the lungs at the end of a normal exhalation or, when a PEEP level is applied, to the end-expiratory lung volume (EELV), which is the sum of FRC and the volume of gas in the lung due to the application of PEEP [21, 34]. There are several methods to measure, directly or indirectly, the lung volume in critically ill patients: the most used are CT scan, helium dilution technique, and washin/washout of a tracer gas (N_2 or O_2). The first two techniques can also be applied to patients on ECMO, while the last one would not be reliable. Today the CT scan is still considered the gold standard, but the dilution technique with helium, which showed an accuracy comparable to that of CT, has the great advantage that it can be performed also at the bedside but requires a brief disconnection of the patient from the ventilator, which may enhance lung derecruitment. The FRC in healthy adults is around 3–3.5 l while in ARDS patients may be lower than 700 ml [22]. Lung volume reduction correlates to the severity of lung disease [21]. Measures of lung volumes may help to evaluate the course of lung disease, to assess the efficacy of recruitment maneuvers and of different levels of PEEP, and to tailor the ventilatory strategy to the real size of the “baby lung” [26, 34].

Recently, lung ultrasound (LUS) is becoming a new tool for daily respiratory monitoring [35]. This bedside, noninvasive and easy repeatable technique offers accurate information that may help the clinician to deal with several different scenarios, such as the diagnosis of pneumothorax, pleural effusion, airways obstruction, parenchymal consolidation and alveolar-interstitial syndromes [35]. Moreover, LUS effectively describes progressive lung de-aeration and re-expansion [36], thus can easily and repeatedly check lung disease progression/resolution [37] and closely monitor any respiratory maneuver, eventually suggested by LUS, aimed at improve lung recruitment [35, 36, 38]. Fig. 21.6 reports the use of lung ultrasound in a patient undergoing VV ECMO in which pressure-volume curves were also obtained.

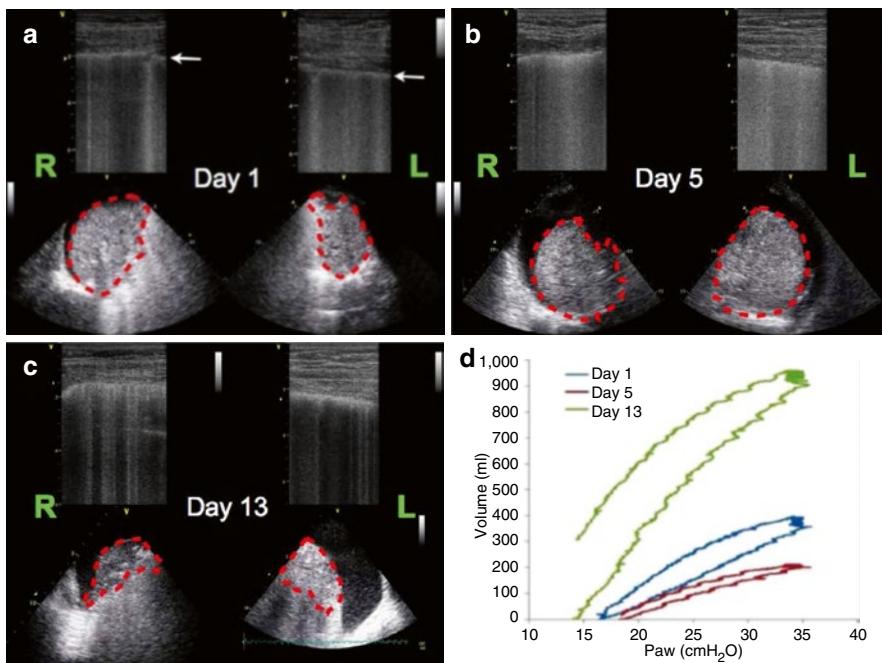


Fig. 21.6 Monitoring of VV ECMO-assisted ARDS varicella pneumonia patient by means of lung ultrasound. (a–c) Quad panels show LUS changes over time in representative ventral (*upper pictures* of each quad panel) and dorsal (*lower pictures* of each quad panel) areas of the lung (transversal scans through the same intercostal spaces, respectively, in the most nondependent and dependent areas, on both lungs; R right, L left). Panel (d) shows P–V curves performed simultaneously to LUS images acquisition. All observations performed on day 1, day 5, and day 13 of ICU stay (ARDS onset occurred 2 days before ICU admission). Panel (a) (day 1): ventral areas show a typical sonographic interstitial syndrome pattern with multiple longitudinal artifacts (B lines) arising from the pleural line (horizontal hyperechoic line, *arrow*) and spreading to the edge of the screen; zones of major crowding, especially on the left scan, can be observed; additional features are represented by pleural thickenings and irregularities and scattered subpleural consolidations (all consistent with an inflammatory origin of the edema). Dorsal areas show complete “hepatization” of the lung, i.e., an LUS pattern of consolidation consistent with complete loss of aeration of the most dependent regions (*dashed areas* highlight the extension of these consolidations). The corresponding P–V curve in panel (d) shows a very low compliance ($Cpl_{RS}=20\text{ ml/cmH}_2\text{O}$) and a limited recruitability, as demonstrated by the small hysteresis of the curve. Panel (b) (day 5): ventral areas now show an increase in B lines crowding, even reaching on the left scan the pattern of “white lung” (complete coalescence). *Dorsal areas* show an increase in the size of consolidations (note the *dashed areas* size) and the appearance of likely abundant pleural effusions (*black, anechoic, layer surrounding the consolidated lung*). The corresponding P–V curve in panel (d) shows now an even smaller compliance ($Cpl_{RS}=13\text{ ml/cmH}_2\text{O}$) and further reduction of recruitability (very small hysteresis of the curve). Panel (c) (day 13): ventral areas finally show a relevant reduction in the number and crowding of B lines, while dorsal ones show a dramatic reduction in consolidated areas size, despite an increase in the pleural effusion amount (thicker anechoic layer). The corresponding P–V curve in panel (d) confirms the relevant improvement of the lungs, as demonstrated by a markedly increased compliance ($Cpl_{RS}=43\text{ ml/H}_2\text{O}$) and a much higher recruitability (wide hysteresis). Patient was successfully weaned from VV ECMO on day 15

21.5 Conclusions

Clinical management of severe ARDS patient undergoing VV ECMO for respiratory support requires a specific monitoring to discriminate the role of extracorporeal gas exchange from the native lung function. This challenge is even more complex since extremely scarce data are present in the literature, and therefore anecdotic data became relevant. Experience of the clinical staff becomes invaluable to understand and interpret the numerous information obtained. We always monitor these patients with a Swan–Ganz catheter that gives us valuable information and a continuous measurement of mixed venous blood saturation. Important technological developments are revolutionizing the way we monitor our patients, especially those undergoing ECMO. The bigger the challenge, the greater the commitment.

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Structure of an ECMO Network for Respiratory Support

22

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and Alberto Zangrillo

22.1 Introduction

In adult patients with respiratory failure refractory to conventional treatment, ECMO represents a potentially lifesaving option, and the CESAR trial indeed indicated that significantly more patients with severe ARDS survived without severe disability if they were transferred to a single ECMO center compared with patients who were managed conventionally at remote hospitals [1, 2]. Nevertheless, several questions still remain to be considered when figuring out a national ECMO network with a structured interhospital transport.

ECMO is a supportive therapy that ensures gas exchange and systemic perfusion, sustains the life of the patient when lung function and the native heart are dangerously compromised, and therefore should be considered to facilitate safe transfer from outlying hospitals to referral centers.

Interhospital transportation of critically ill patients to referral centers is required when local resources and technology are insufficient for adequate management. Moreover, many patients requiring transfer are often too unstable to undergo conventional transport [3]. Cannulation is performed on site by the retrieving team, and the patient is stabilized before transportation. The process requires a specialized team and resources dedicated to retrieval. Therefore, as ECMO is an invasive, intensive form of support, it requires considerable institutional commitment. Consequently, its use is advocated only in those patients believed to be at substantial risk of death.

In Australia and New Zealand, during the 2009 influenza A(H1N1) winter pandemic, there was a large increase in the use of ECMO for ARDS in patients compared with the winter of 2008, which was predominantly explained by the high

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number of patients who were transported on ECMO. Despite their illness severity and the prolonged use of life support, most of these patients survived [4].

Establishing explicit criteria for patient selection, timing of ECMO initiation, and optimal and safe application are first steps toward the validity of ECMO for adults with ARDS.

Could a network organization based on preemptive patient centralization allow a higher survival rate of patients with severe ARDS?

22.1.1 Network Organization

The recent epidemics, severe acute respiratory syndrome (SARS) and pandemic influenza A H1N1, have highlighted the potential for respiratory viral infections to cause severe disease with a significant risk of mortality. However, several other viruses cause significant respiratory morbidity annually and have the potential to produce epidemics [5].

Mortality can be reduced by adequate preparation, preventive measures, and specific plans for the organization of ICU services. The European Society of Intensive Care Medicine Task Force suggested recommendations and standard operating procedures for the ICUs [6].

In 2009, the Italian Ministry of Health established a national network of selected ICU centers, the Extracorporeal Membrane Oxygenation Network (ECMONet), and ensured economical, human, and technological resources. Two competent physicians guided ECMONet organization and development. The ECMONet organization is officially operational since November 5, 2009. The Italian network was set up to centralize all potentially severe patients in a limited number of tertiary hospitals to provide advanced treatment options including ECMO and identify predictors of mortality in order to define the best timing of ECMO institution.

The network consisted of 14 ICUs with ECMO capability and a national call center.

The ICU centers were selected based on their (1) experience in treating ARDS patients, (2) experience in respiratory ECMO or presence of a cardiac surgery team expert in ECMO, and (3) territorial distribution. Five centers ensured the interhospital transport through the whole Italian territory whenever the nearest ECMONet center could not handle a case. The national ECMONet Call Center Service screened all requests from any hospital in Italy and directed them to the closest ECMONet center and/or to the transportation ECMO team.

Sessions of ECMO training course, open to physicians, perfusionists, and nurses of the ECMONet, were organized [7].

22.1.2 Patient Selection and Referral to the ECMONet

National recommendations and procedures for patient referral to the ECMONet (Table 22.1 and Fig. 22.1) and ECMO eligibility criteria (Table 22.2) were enacted by the Italian Ministry of Health and communicated to all local sanitary authorities and to the administration of all Italian hospitals.

Table 22.1 Recommended national clinical criteria for early patient centralization

<i>From primary and secondary hospitals to tertiary hospitals with ARDS treatment experience</i>	
Suspected H1N1 infection with one of the following:	
1. Need for invasive mechanical ventilation with PEEP 2. $\text{FiO}_2 > 0.6$	
<i>From any non-ECMO center to ECMOnet centers</i>	
Suspected H1N1 infection with one of the following:	
1. $\text{HbO}_2 < 85\%$ 2. $\text{OI} > 25$ 3. $\text{PaO}_2/\text{FiO}_2 < 100$ with $\text{PEEP} \geq 10 \text{ cm H}_2\text{O}$ 4. Hypercapnia and respiratory acidosis with $\text{pH} < 7.25$ 5. SvO_2 or $\text{SvCO}_2 < 65\%$ despite $\text{Ht} > 30$ and administration of vasoactive drugs	
<i>PEEP</i> positive end-expiratory pressure, <i>FiO₂</i> inspired oxygen fraction, <i>HbO₂</i> oxygenated hemoglobin, <i>PaO₂/FiO₂</i> arterial partial pressure of oxygen to <i>FiO₂</i> ratio, <i>OI</i> oxygenation index (computed as <i>FiO₂</i> × mean airway pressure × 100/ <i>PaO₂</i>)	

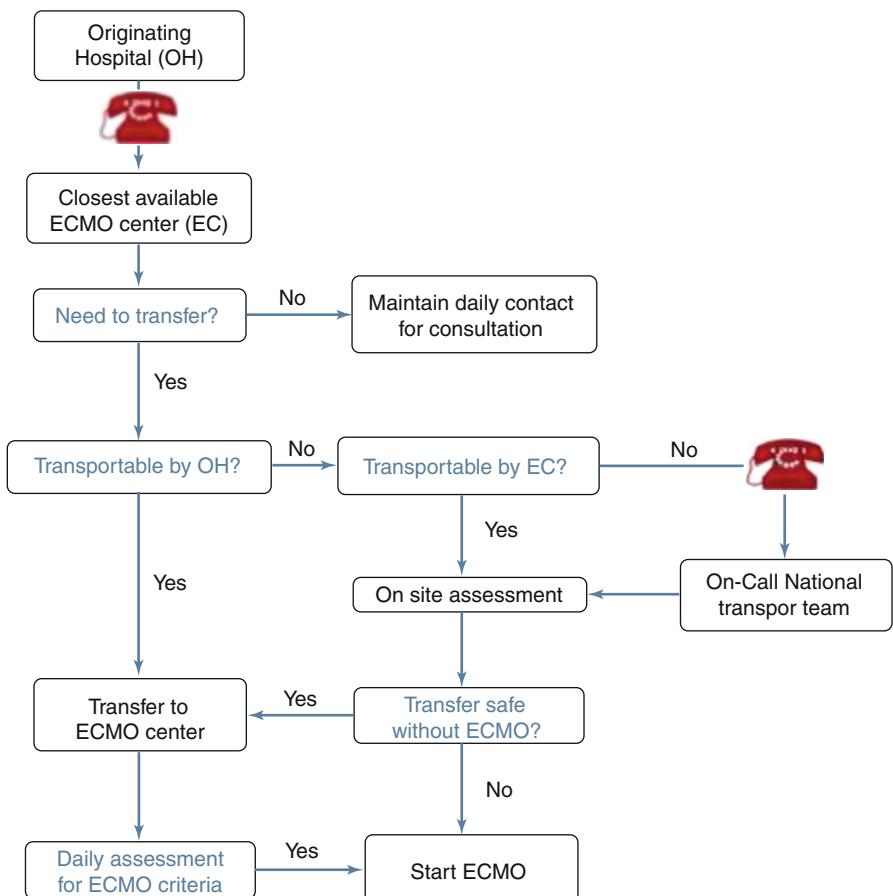


Fig. 22.1 Management algorithm for the referrals to the Italian ECMOnet system

Table 22.2 Recommended national clinical criteria for ECMO eligibility*ECMO inclusion criteria*

All adult and pediatric patients with severe ARDS related to suspected influenza A(H1N1) presenting with at least one of the following criteria despite the use of available rescue therapies:

1. OI >30
2. $\text{PaO}_2/\text{FiO}_2 < 70$ with PEEP $\geq 15 \text{ cm H}_2\text{O}$ (in patient already admitted to one of the ECMOnet centers)
3. $\text{PaO}_2/\text{FiO}_2 < 100$ with PEEP $\geq 10 \text{ cm H}_2\text{O}$ (in patients still to be transferred)
4. pH <7.25 for at least 2 h
5. Hemodynamic instability

ECMO exclusion criteria

Absolute

1. Intracranial bleeding or other major contraindication to anticoagulation
2. Previous severe disability
3. Poor prognosis because of the underlying disease (i.e., unresolved malignancy)

Relative

1. MV >7 days

PEEP positive end-expiratory pressure, *FiO*₂ inspired oxygen fraction, *PaO*₂/*FiO*₂ arterial partial pressure of oxygen to *FiO*₂ ratio, *OI* oxygenation index (computed as *FiO*₂ × mean airway pressure × 100/*PaO*₂), *MV* mechanical ventilation

If required, an ECMOnet team (2 ICU physicians, 1 perfusionist, 1 ICU nurse) traveled to the referring hospital to take care of the transfer. After an attempt to stabilize/improve the status of the patient, the ECMOnet team would decide to either transport the patient conventionally or establish ECMO at the referring hospital. Transportation was carried out via ambulance, helicopter, or fixed-wing aircraft, depending on distance, weather conditions, and ECMOnet center resources [7].

22.1.3 ECMO Team, Ventilator Management, and Safety

The ECMO retrieval team must be very skilled and equipped for both venovenous VV ECMO and venoarterial VA ECMO. Percutaneous peripheral VV ECMO is preferred when cardiac function is adequate or mildly depressed. Patients should always be initiated on VV and eventually transitioned to VA ECMO if cardiac support is required. Vessel cannulation for VV ECMO can be configured in several ways: dual-site or single-site approach. Beyond the hemodynamic instability, the ECMO team also will have to assess other conditions such as severe obesity and bleeding.

Some basic facilities are required in peripheral hospitals to ensure safety: echocardiography, fluoroscopy, surgery, and blood bank. The use of a bicaval dual-lumen cannula is recommended only if a safe environment is available [8]. Settings of mechanical ventilation for patients on VVECMO should minimize ventilator-associated lung injury and permit higher degrees of protective lung ventilation.

Initiation and target for anticoagulation during transport depend on the availability of ACT. Bleeding should be thoroughly assessed before leaving the remote hospital.

22.1.4 ECMOnet Activity

Between August 2009 and March 2010, 153 critically ill patients with suspected H1N1 were admitted to the ICUs of the 14 ECMOnet centers, of which 81 patients were referred from other hospitals. 71 patients were transferred by ambulance (19 on ECMO), 8 by helicopter (all on ECMO), and 2 by fixed-wing aircraft (1 on ECMO). All patients were transported successfully and without complications to the referral hospital.

Sixty patients (median age 39.7 ± 12 , 60 % were male) received ECMO (59 VV ECMO and 1 VA ECMO) according to ECMO eligibility criteria. All patients fulfilled criteria for ARDS. Median duration of MV (mechanical ventilation) before ECMO was 2 (1–5) days in patients with confirmed H1N1 (ARDS_{H1N1}) and 8 (1–14) days in patients with other causes of ARDS (ARDS_{other}). Before ECMO, 42 patients (70 %) had received at least one “rescue therapy” (recruitment maneuvers, prone positioning, high-frequency oscillatory ventilation, inhaled nitric oxide, vasoactive drugs, steroid therapy). There were no statistically significant differences between ARDS_{H1N1} and ARDS_{other} in terms of severity of respiratory failure, treatment, and nonrespiratory organ function before ECMO.

Survival to hospital discharge in patients receiving ECMO was 68 %. Survival of patients receiving ECMO within 7 days from the onset of mechanical ventilation was 77 %. Survival rate in patients transported on ECMO was 81 %. There were no statistically significant differences between patients transported on ECMO and patients starting ECMO at the ECMOnet center in terms of severity of respiratory failure, treatment, and outcomes. The length of MV prior to ECMO was an independent predictor of mortality.

Among the 60 patients who received ECMO, 49 (82 %) ARDS_{H1N1} presented a survival rate of 71 %, the remaining 11 (18 %) ARDS_{other} presented a survival rate of 54 %. The median duration of ECMO support was 10 (7–17) days in ARDS_{H1N1} and 8 (3–21) days in ARDS_{other}.

Sixteen patients had hemorrhagic complications, and in 10 of them, a major bleeding event occurred, requiring blood transfusions and temporary reduction or suspension of anticoagulation. One patient died of cerebral hemorrhage diagnosed 2 days after cannulation. Blood components were transfused in 47 (78 %) patients.

Multiple organ failure associated with sepsis was the most common cause of death (53 %), followed by septic shock (26 %). All nonsurvivors were still on ECMO at the time of death [7].

22.1.5 ECMOnet Score

All baseline patient characteristics, clinical parameters, and vital signs before ECMO initiation were tested by univariate analysis. Using multivariate analysis, we identified five statistically significant predictors of death: preECMO hospital length of stay, bilirubin value, creatinine level, hematocrit value, and systemic mean arterial pressure.

The ECMOnet score was developed based on these variables. With the aim to be as intuitive as possible, the score was constructed to give a result between 0 and 10

Table 22.3 The ECMOnet score

Parameter	Partial score
<i>PreECMO hospital length of stay (days)</i>	
≤3	0.5
4–7	1
8–11	1.5
>11	2
<i>Bilirubin (mg/dl)</i>	
≤0.15	0
0.16–0.65	0.5
0.66–1.15	1
1.16–1.65	1.5
1.66–2.15	2
>2.15	2.5
<i>Creatinine (mg/dl)</i>	
≤0.5	0
0.51–0.8	0.5
0.81–1.10	1
1.11–1.14	1.5
1.41–1.7	2
1.71–2.0	2.5
2.01–2.3	3
>2.3	3.5
<i>Hematocrit (%)</i>	
>40	0.5
36–40	1
31–35	1.5
≤30	2
<i>Mean arterial pressure (mmHg)</i>	
>90	0
61–90	0.5
≤60	1

ECMO extracorporeal membrane oxygenation

(Table 22.3). Thus, the number resulting from score calculation can be easily associated with the mortality risk. A score of 4.5 was found to be the most appropriate cutoff for mortality risk prediction. The high accuracy of the ECMOnet score was further confirmed by ROC analysis and by an independent external validation analysis [9].

22.2 Comment

The role of ECMO in ARDS is now well-defined: ECMO support should be considered in patients with respiratory failure refractory to conventional therapy not only to ensure gas exchange but also to minimize ventilator-associated lung injury and its associated multiple organ dysfunction, both crucial determinants of survival for patients with ARDS. Several reports demonstrated that ECMO can be undertaken without the prohibitive morbidity and adverse events seen in the 1970s.

To be effective, ECMO must be applied to the appropriate patient (indications, contraindications), timing of ECMO initiation must be the most correct (not too early, not too late), and ECMO must be correctly and safely applied (patient considerations: age, obesity, VV or VA ECMO, dual-site or single-site venovenous cannulation; monitoring and general measures—ultrasound, fluoroscopy, surgery, and blood bank).

The centralization of patients to a few selected, specifically equipped centers can improve patient outcome, but the risks associated with patient transportation could exceed the benefits of centralization [10]. To reduce these risks, we planned some strategies: transferring in advance the largest proportion of patients potentially at risk of severe respiratory deterioration according to clinical criteria and assigning the patients to expert transportation teams, able to institute ECMO at the referring hospital and provide safe transportation with ECMO according to precise criteria. Some of the patients transported with ECMO might not have needed ECMO if treated from the beginning with other rescue therapies at the referral centers, where more therapeutic options were available. However, most of these patients were considered to be not safely transportable without ECMO.

The Italian ECMO network ensured a high survival rate of patients with severe ARDS due to H1N1 infection treated by ECMO, a safe centralization, and created an organization ready to challenge future possible epidemics with high demand for critical care units with advanced respiratory support [7]. CESAR randomized trial indicated that significantly more patients with severe ARDS survived without severe disability if they were transferred to a single ECMO center compared with patients who were managed conventionally. Moreover, this trial showed that patients referred for ECMO had roughly two times longer hospital stays and twice the medical costs of those treated in the conventional management group [1]. One or two patients with influenza A (H1N1)-related ARDS can strain the capacity of any intensive care unit (ICU) and ECMO team, particularly when ECMO availability is needed for other patients. ECMO centers should make plans for allocation of resources: identification of early predictors of adverse outcome could allow optimization of criteria for ECMO eligibility and referral.

The Italian ECMOnet activity showed that mortality of adult patients suffering from influenza A (H1N1)-related ARDS undergoing VV ECMO is related to extrapulmonary organ function at the time of cannulation. PreECMO hospital length of stay; bilirubin, creatinine, hematocrit values; and systemic mean arterial pressure were significantly associated with mortality as assessed by multivariate analysis, while respiratory parameters were not associated with survival.

To improve risk stratification and prediction of mortality risk at time of VV ECMO initiation, we developed a multifactorial scoring system—the ECMOnet score [9].

These data provide new perspectives concerning the allocation of resources for VV ECMO. We confirm the strong clinical perception that survival is strongly correlated to extrapulmonary organ function at the time of ECMO initiation. This knowledge may help to identify potential candidates for ECMO support according to their mortality risk and provides guidance to solve crucial economic and ethical issues.

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Alia Noorani and Alain Vuylsteke

23.1 Introduction

Extracorporeal cardiopulmonary support was conceptually born in 1930. John Gibbon, a recently qualified doctor, saw a young patient die of a massive pulmonary embolus following cholecystectomy. He understood that temporary mechanical support of the cardiopulmonary system may have possibly saved her life during the embolectomy. It is in 1953 that he successfully pioneered the use of an artificial oxygenator and perfusion system to perform the first successful open heart procedure: an atrial septal defect repair in an 18-year-old female [1].

A further decade lapsed before it was apparent that cardiopulmonary bypass (CPB) was not ideal to support patients for the long term. In 1971, Donald Hill and colleagues successfully supported for 75 h a 24-year-old patient with acute post-traumatic respiratory failure following blunt trauma [2].

In 1974, a thoracic surgeon named Robert Bartlett and his colleagues developed the concept of extracorporeal membrane oxygenation (ECMO) whilst treating neonates with respiratory distress syndrome. They successfully supported a neonate with meconium aspiration syndrome with an entirely experimental extracorporeal membrane oxygenator. The support lasted for 3 days and the neonate made a full recovery [3].

With variations in cannulation, complete cardiopulmonary (veno-arterial, VA ECMO) or respiratory support alone (veno-venous VV ECMO) can be provided. The versatility and cardiorespiratory safety provided by ECMO has made

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bridging to recovery, decision or transplantation in respiratory failure or cardiogenic shock possible. Its use has made complicated thoracic surgical procedures feasible by providing complete pulmonary isolation even in patients with poor respiratory reserve. Thoracic procedure that can be supported by ECMO ranges from lung resections to airway surgery, including bridge to lung transplantation and rescue therapy if required after transplantation.

23.2 General Principles for Cannulation

23.2.1 In Adult Patients

VV ECMO is preferred for adults with respiratory failure with minimal cardiac depression.

VA ECMO is the preferred option in the face of moderately or severely depressed myocardial function. Recent advances in technology and equipment include the development and use of the Avalon (Avalon Laboratories, LLC, California) cannula, which comprises a single cannula for both venous drainage and return of oxygenated blood to be placed under fluoroscopic control into the right atrium, via a Seldinger technique in the internal jugular vein. Alternately, two or more venous sites can be used. Peripheral VA ECMO can be achieved via the femoral artery and vein route [4].

23.2.2 In Paediatric Patients

VV access can be achieved via a double-lumen catheter placed into the right atrium via the internal jugular vein for patients weighing less than 15 kg or via either the femoral vein or the right internal jugular vein. VA cannulation is performed via a femoral artery and the right internal jugular route with other venous cannulas being inserted into an unused femoral or internal jugular vein [4].

23.3 Thoracic Surgery Facilitated by ECMO

23.3.1 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia is a life-threatening condition that often requires ECMO support for repair. Intrathoracic hypertension and subsequent cardiorespiratory compromise caused by displaced abdominal viscera can leave the neonate susceptible to cardiopulmonary collapse. The use of VA or VV ECMO in these cases enables safe conduct of operative repair.

Although the optimal timing of ECMO (pre-repair versus during repair) has been widely speculated, with varying results, a recent study by Bryner et al. in 2009 showed improved outcomes for patients who underwent surgery after a period of

stabilisation followed by liberation from ECMO [5]. Regardless of timing, studies have repeatedly shown that ECMO support improves survival compared to no support [6]. Guner et al. compared cannulation options and type of support offered and found that VA and VV ECMO were comparable with the added benefit of preserving the carotid artery in the VV group [7].

23.3.2 Airway Surgery

Airway surgery can pose significant challenges and obstacles for both the surgeon and the anaesthetist, as patients undergoing tracheal resections are at a real risk of cardiovascular collapse. Indications for surgical resection include tracheal stenosis commonly caused by endotracheal intubation, burns, trauma as well as tracheal malignancies. Several cases of successful institution of VV ECMO have been described, with cannulation via the femoral vessels. These cases have included resection of tracheal papillomas as well as for tracheal rupture following endotracheal intubation and blunt trauma [8–10]. In addition, ECMO may facilitate healing without the risk of anastomotic injury from positive pressure ventilation.

23.3.3 Mediastinal Masses

ECMO may be beneficial in cases where large anterior mediastinal masses (e.g. thyroid goitres) can cause airway compression and a significant risk of death when the patient is paralysed to facilitate endotracheal intubation. ECMO may be instituted under light sedation or local anaesthesia, even in the upright position [1].

23.3.4 Surgery for Pulmonary Embolism

Cardiorespiratory failure due to massive pulmonary embolism can be successfully managed with ECMO if this is instituted expeditiously, before neurological injury ensues. Usually 48–72 h of support is sufficient, by which time the emboli have moved into segmental branches. At this time point, successful liberation can be achieved and patients managed with thromboprophylaxis and a vena caval filter. Conversely if there is little or no cardiopulmonary recovery after this time, pulmonary embolectomy may be performed, with ongoing ECMO support postoperatively until normal lung function returns [1].

23.3.5 Pulmonary Infections

Posttraumatic empyema following bony fractures, subsequent pulmonary contusions and haemothorax has been successfully treated with thoracotomy, lung isolation via single-lung ventilation and VV ECMO. In a case similar to the very first

ECMO case, Brenner et al. reported a successful case of a 45-year-old male involved in a motorcycle collision, who presented with bilateral pulmonary contusions and a left haemothorax. Intensive care stay was protracted due to ventilator-associated pneumonia and the development of a left-sided empyema. Successful thoracotomy and decortication with concurrent VV ECMO support was possible with vascular access via the femoral and internal jugular veins. This demonstrates the feasibility of surgery in high-risk patients [11].

Souilamas et al. reported a case of pulmonary aspergilloma resistant to medical treatment and embolisation therapy, presenting with recurrent haemoptysis. The patient's preoperative lung function was borderline, with an FEV1 of 42 % and left lung perfusion of 75 %. Single-lung ventilation was considered difficult, and the risk of postoperative respiratory failure was high. VV ECMO was instituted via single-site cannulation using the Avalon cannula, and uneventful segmentectomy was performed with ECMO support being weaned after 12 h following surgery [12].

23.3.6 Cancer

An unusual application of ECMO has been used as support for lung cancer surgery. Kondo and colleagues in Japan described two cases of left sleeve pneumonectomy for adenocarcinoma of the left main bronchus successfully resected with ECMO support [13]. Lei and colleagues reported a case of a 55-year-old man who presented with haemoptysis 10 months following left pneumonectomy for squamous cell carcinoma. Bronchoscopic findings demonstrated blood in the left bronchial stump, and biopsy samples confirmed adenosquamous carcinoma. His risk of imminent asphyxiation encouraged them to consider carinal resection and reconstruction under ECMO support. Cannulation was via an ipsilateral femoral artery and vein, and the patient was successfully discharged home 10 days following surgery [14].

23.3.7 Trauma

ECMO has been instrumental in successful salvage of a case of penetrating chest trauma. Massive haemorrhage from a laceration to the lung parenchyma was controlled with massive transfusions and surgical repair. Subsequent transfusion-associated lung injury was managed with VV ECMO support [15].

23.3.8 Bridge to Lung Transplant (BTT)

Pre-transplant mechanical ventilation has been shown to be a significant predictor of post-mortality, and as patients on ECMO may fall into this category, many have been denied transplantation and have subsequently died. Recent results, however,

from many centres have demonstrated that patients on ECMO as a BTT have excellent survival rates, comparable to non-ECMO patients. For this reason in general, it is advocated that carefully selected patients be offered a chance of transplant whilst on ECMO preoperatively [16].

23.3.9 Post-lung Transplant Support

Primary graft dysfunction (PGD) following lung transplantation may occur due to a number of factors ranging from surgical technique and trauma, borderline donor organs or donor organ preservation, denervation injury or rejection. Despite being subject to much research and study, survival remains poor in this subgroup of patients, with registry data from the International Heart and Lung Transplantation Society demonstrating that PGD is responsible for up to a third of all deaths within 90 days following transplantation [17].

Several advantages for ECMO may be evident in these cases. Firstly, high FiO_2 is not necessary, thereby limiting toxicity and barotrauma to the implanted lung; secondly, ECMO can produce a lowered capillary hydrostatic pressure thereby limiting oedema. Finally, if re-transplantation is considered, ECMO can provide support to the patient as a bridge to re-transplantation. Survival figures of up to 88 % have been reported with the use of VV ECMO for PGD, and these compare favourably with the 94 % survival rate for lung recipients within 30 days of surgery [17]. Advancements in technology and therapy mean that this form of support is no longer considered as salvage intervention.

23.3.10 Bronchopleural Fistula or Massive Air Leak

Massive air leak in which less than half the inspired volume is expired out can be an indication for VV ECMO. The first principle of any air leak management is to evacuate air from the pleural space to allow approximation of lung to the chest wall, creating adhesions. With ECMO, chest tube placement and application of suction is necessary followed by limitation of inspiratory pressure and volume. Larger air leaks may be initially managed in the same way, followed by video-assisted or open surgery to aid in closure. In an example of this scenario, Oey et al. describe a case of air leak management in a difficult case whereby a 55-year-old man with a previous right pneumonectomy for squamous cell carcinoma developed emphysema of his remaining lung. He presented acutely to the emergency department with increasing dyspnoea, whereby a large bulla in the only lung was mistaken for a pneumothorax. Chest drain placement into this bulla led to impending respiratory failure due to the massive air leak. In view of his poor respiratory reserve and previous surgery, single-lung ventilation was not an option and VV ECMO support was instituted, with concomitant VATS repair of the air leak. ECMO support was successfully discontinued within hours postoperatively, the patient being discharged in 5 days [18].

23.3.11 Pulmonary Thromboendarterectomy

ECMO has been used successfully to bridge and support patients undergoing pulmonary endarterectomy [19] and in patients recovering from pulmonary endarterectomy and suffering from reperfusion injury [20].

23.4 Thoracic Surgery on the ECMO Patient

Thoracic surgical procedures are sometimes necessary in the ECMO patient, and these can be particularly hazardous due to ongoing need for anticoagulation and detrimental effects of the circuit on platelets and the coagulation cascade. In the largest series of ECMO patients investigated over a 16-year period, the Leicester group retrospectively reviewed 569 patients on ECMO and determined that the need for thoracotomy whilst on ECMO was 3.2 %, with 40 thoracotomies performed in 18 patients (19 were primary operations and 21 were reexplorations). The commonest indication for thoracotomy was bleeding post chest drain insertion (58 %), followed by uncontrolled air leak in 47 % and pleural effusion in 21 %. The commonest primary operation was evacuation of haemothorax in 63 % of patients. The authors noted that although the overall need for thoracotomy was 3.2 %, the in-hospital mortality was considerable, at 39 %. For this reason they advocated that ECMO specialists either have thoracic surgical experience or have thoracic surgeons present on-site in ECMO centres [21].

23.5 Complications of ECMO Used to Facilitate Surgery

These will be covered in more detail in other chapters in this book. Essentially, however, they can be categorised into the following:

1. Vascular injury from cannulation
 2. Air embolus
 3. Excessive bleeding due to platelet dysfunction or coagulation deficiencies
 4. Haemolysis from the mechanical effects of the pump on red blood cells
-

23.6 Conclusion

ECMO has come a long way from Gibbon's first thoughts in 1930, and significant technological advances have enabled its versatile use in the adult and paediatric population in supporting the cardiopulmonary circulation. From a thoracic surgical perspective, the safety provided by the level of support has encouraged more and more diverse use of this technology and has made many more patients eligible for surgery than ever before.

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24.1 Awake ECMO: Why? On Which Patients?

Extracorporeal membrane oxygenation (ECMO) could be the more reasonable supportive treatment of acute respiratory. By using an artificial organ to temporarily replace the failing lung, not only we can favor lung recovery by allowing organ rest, but in some patients we can even avoid intubation, thus preventing the well-known complications associated with invasive mechanical ventilation (IMV).

However, for a long time the approach of replacing the failing native lung with an artificial organ has not been widely applied, due to the invasiveness, costs, and complexity of the extracorporeal technique. ECMO was used only as a complement to IMV, in those relatively rare patients with persistent refractory impairment of gas exchanges despite the optimization of mechanical ventilation settings [1]. However, in the last decade ECMO has evolved into a less invasive, less dangerous, and user-friendly technique [2], and for this reason some groups began to consider ECMO as a reasonable alternative to IMV in selected groups of patients, thus breaking the paradigm of IMV as the inevitable treatment of severe respiratory failure. “Awake ECMO” is the name frequently used to indicate this alternative approach of using ECMO without IMV.

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Up to 2010, published reports of ECMO in awake, non-intubated patients were very limited: of note, only two pediatric cases of malignant mediastinal masses treated with femorofemoral venoarterial ECMO (vaECMO) [3] and one case of a papillomatous carinal mass treated with femoro-jugular venovenous ECMO (vvECMO) [4] were reported. In those cases, ECMO was used as a primary respiratory support without intubation in order to avoid the severe risk of total airway collapse associated with induction of anesthesia, intubation, and paralysis.

In the last years, the most important indication for awake ECMO has been as bridge to lung transplantation [5–7]. The application of awake ECMO as bridge to lung transplantation aims at avoiding, if possible, the unfavorable cascade that, starting with intubation and sedation, involves muscle deconditioning, neuromuscular complications, hospital-acquired infections, and hence poor outcome even when the patient eventually receives the graft.

Recently, awake ECMO has been successfully used also as a bridge to recovery from acute respiratory failure [8], especially in patients in whom the risk associated with IMV was considered particularly high, like immunocompromised or COPD patients [9].

24.2 Awake ECMO: When?

Awake ECMO, the “differently invasive” alternative to intubation and IMV, can be used:

- As a planned early choice, in patients in which the respiratory support provided by IMV alone is predicted as insufficient, or severely injurious for the lungs, or involving a severe risk due to intubation.
- In established or resolving respiratory failure, with IMV already supplemented by ECMO; in some patients, if ECMO was uneventful and is running smoothly, it may be questioned whether the endotracheal tube is still really needed or if it is advisable to maintain the extracorporeal support to help weaning from mechanical ventilation first and only later proceed to weaning from ECMO.

24.3 Anesthesia During Cannulation for Planned Awake ECMO

Cannulation for planned awake ECMO can be performed under local or general anesthesia. The choice should be tailored on each individual patient.

If the clinical condition is reasonably stable and the patient is cooperative, cannulation can be performed under local anesthesia and on noninvasive ventilation (NIV). Awake cannulation can be a judicious choice also in very severe patients in which muscle relaxation and intubation are expected to be potentially catastrophic, like in some patients with advanced lung fibrosis or cystic fibrosis, totally dependent on NIV.

However, planned awake ECMO does not necessarily mean that the patient must be awake during cannulation. In most cases, a safe and practical approach consists in cannulating the patient under general anesthesia, followed by extubation within few hours, after stabilization.

24.4 By Which ECMO Mode?

Awake ECMO has been applied in several different configurations, as pumpless arteriovenous (av) bypass, as vvECMO, as vaECMO, and even as pumpless bypass on the pulmonary circulation.

The pumpless av approach requires the femorofemoral implantation of a specific low-resistance artificial lung, the Novalung® interventional lung assist (ILA®). This is the easiest way to provide an extracorporeal respiratory support in an awake patient and has been used as a bridge to lung transplantation in patients with good cardiac function [10]. A 15-F arterial cannula combined with a 17-F venous cannula can provide a blood flow to the ILA® of approximately 1.5 l/min. This blood flow, combined with hyperventilation of the artificial lung with up to 10 l/min of oxygen, can provide a powerful carbon dioxide (CO₂) removal of 200–250 ml/min. However, the oxygenation capacity of this approach is minimal [11]. Therefore, the indications are limited to patients in which CO₂ elimination is the main problem, while oxygenation can be effectively compensated by inhalation of supplemental oxygen, with or without NIV or noninvasive continuous positive airway pressure (CPAP).

vvECMO is the most widely used mode for extracorporeal support in non-intubated patients. vvECMO can easily obtain a CO₂ removal equal to the entire metabolic production (Fig. 24.1), with significant reduction of respiratory drive in terms of both frequency and amplitude [9]; this translates into a reduction of the work of breathing and oxygen consumption and thus may also indirectly improve oxygenation. The direct effect of vvECMO on oxygenation depends mainly on the balance among cardiac output, extracorporeal blood flow rate, and recirculation rate and hence on size, type, and position of the cannulas. With a 23-F jugular bi-caval double-lumen Avalon Elite® cannula and an extracorporeal blood flow of 2.5 l/min, it is possible to obtain an oxygen transfer of approximately 100 ml/min in a spontaneously breathing adult [12]. A much higher oxygen transfer, even approaching the level of the metabolic oxygen consumption, can be obtained with a cannulation setup enabling a higher extracorporeal blood flow with limited recirculation. The choice of the cannulation approach strongly affects the oxygenation power of vvECMO; as a consequence, the patient might either need just an inhaled oxygen supplementation or require positive pressure to improve alveolar recruitment and oxygen transfer by the native lung.

The awake vaECMO approach has been used when lung failure was associated with severe pulmonary hypertension and right heart failure. In a recent report of vaECMO as a bridge to recovery or to heart transplantation for primary cardiogenic shock or cardiac arrest [13], the treatment protocol recommended awake ECMO, if possible, especially when a need for prolonged extracorporeal support was

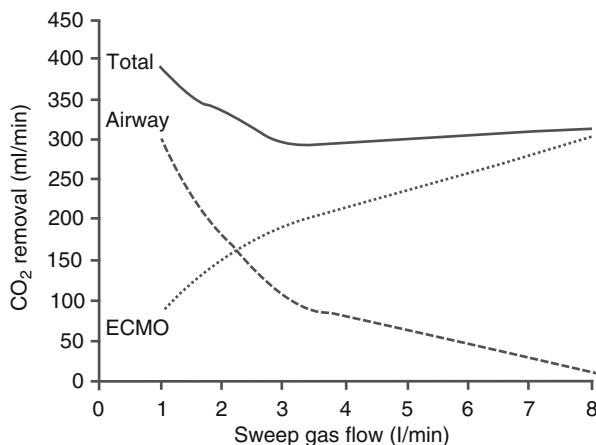


Fig. 24.1 CO₂ removal at different levels of sweep gas flow (SGF) during awake vvECMO. Increasing levels of SGF were associated with an increase of extracorporeal CO₂ removal and a simultaneous decrease of the CO₂ removed by the lungs. The decrease in total CO₂ removal observed between 1 and 3 l/min of SGF resulted from a decrease in oxygen consumption (and metabolic CO₂ production) due to the drop of a high work of breathing. At an SGF of 8 l/min, the metabolic CO₂ production was nearly totally removed by the artificial lung

foreseen. In this report of 16 patients with a 50 % survival at hospital discharge, 29 % of 3,514 h on ECMO was spent as awake ECMO, and 4 patients were never intubated. This report shows that a strategy of awake ECMO, with the purpose of reducing the risk of infection and with the advantage of easy and prompt neurologic assessment, is feasible in several patients with cardiogenic shock.

Finally, in cases of severe chronic pulmonary hypertension, a bridge to lung transplantation has been obtained by surgical central implantation of a Novalung® ILA® in parallel to the pulmonary circulation, between the pulmonary artery and either the left atrium [14] or a pulmonary vein [15]. This pumpless approach, denoted as “paracorporeal artificial lung” (PAL), is made possible by the combination of a powerful hypertrophic right ventricle with the low resistance typical of the ILA® oxygenator. Once stabilized after PAL implantation, patients were extubated and maintained awake up to lung transplantation [14, 15].

24.5 Cannulation Sites

The choice about cannulation sites partly depends on whether or not the clinical staff is oriented to implement a program of active physical therapy including patient ambulation. If this is the case, the femoral vessels cannot be used, and vvECMO has been commonly applied through the right internal jugular vein with a bi-caval double-lumen Avalon Elite® cannula [8, 12, 16–18]. In patients needing a substantial oxygenation support and hence a high blood flow, a very large cannula (27–31 F) must be implanted, but its prolonged use is frequently complicated by deep

vein thrombosis of the upper extremities [19]. The cannula can be stabilized by tunnelization of the right jugular access [12] or by using a left subclavian access [20]. An upper-extremity approach suitable for ambulation has also been used in one case of vaECMO, by using the left axillary vein and artery [21].

The alternative approach with two femoral cannulas, although not compatible with ambulation, does not impede active physical therapy in bed, even including the lower extremities. Usually total leg immobility is unnecessary, and the long wire-reinforced cannulas used for femorofemoral ECMO do not kink with moderate thigh flexion. In our practice, we recommend leg rest only in case of bleeding through the cannula insertion points. The bi-femoral approach is used for both vvECMO and vaECMO and is very practical in patients who need CPAP to improve oxygenation; the free neck allows application of helmet CPAP [22], which is much better tolerated than masks and is the perfect interface for a prolonged treatment.

Whether or not the awake patient on ECMO should also be enabled to ambulate, it is questionable. Walking while on ECMO may expose the patient to additional risks and requires assistance by extra personnel. In a recent Italian report of ECMO as bridge to lung transplantation, patients bridged with awake ECMO had much lower morbidity and an easier clinical course, with less need of postoperative IMV, shorter posttransplant length of stay both in ICU and in hospital, and a lower incidence of critically ill polyneuropathy/myopathy than intubated patients [7]. In this group of patients, awake ECMO was always applied with femoral cannulation; therefore, it can be inferred that the advantages of awake ECMO are maintained, at least partly, even if the ambulation option is excluded.

As already mentioned, the femoral approach is the most practical way to apply a pumpless av bypass, while the PAL in parallel to the pulmonary circulation obviously requires a central cannulation.

24.6 Management of Awake ECMO

24.6.1 Setup and Start

Power and stability of the extracorporeal system are the two keystones for effectiveness and good tolerance of the treatment, and this is particularly important in awake patients, who have the ability to react to the changes in the artificial lung function.

The amount of extracorporeal CO₂ removal can be easily regulated by changing the sweep gas flow of the artificial lung (Fig. 24.1). Extracorporeal CO₂ removal and oxygen transfer decrease patient's need of alveolar ventilation and hence respiratory drive and work of breathing [9]. If ECMO is working properly, shortly after start, the patient feels much better, perceiving the function of the implanted artificial lung like an apparent rapid improvement of the impaired function of his/her native lung. In turn, in case of drop of extracorporeal support performance due to technical problems, the patient will suddenly feel and react like suffocating.

In order to achieve a favorable interaction, it is important to choose the extracorporeal support according to the failing function of the native lung. If the

oxygenation impairment is very severe, it is fundamental to implant large-size canulas, in order to allow the setting of a high extracorporeal blood flow with good stability and without excessive negative/positive pressures. When CO_2 elimination is the major problem, especially if lung compliance is very low, it is important to set an adequately high ventilation of the artificial lung in order to deeply depress the respiratory drive. The resulting reduction of a previously extremely high work of breathing will involve a decrease of the patient's oxygen consumption, thus rising venous oxygen saturation and hence contributing to improve arterial oxygenation. Moreover, the reduction of metabolic CO_2 production (Fig. 24.1) will further contribute to unload the patient.

However, unless the patient is breathing pure oxygen with adequate CPAP, excessive CO_2 removal with vvECMO may result in oxygen desaturation due to alveolar hypoventilation and derecruitment, as a consequence of excessive depression of the respiratory drive. In the clinical case of Fig. 24.2, this is what happened on day 1 with a gas flow of 6 l/min and on day 7 with a gas flow of 8 l/min (corresponding to an extracorporeal CO_2 removal of 192 and 208 ml/min, respectively).

In some patients bridged to lung transplantation for advanced lung fibrosis, lung compliance can be so low that every breath is associated with deep inspiratory breathing efforts: in these cases, extracorporeal CO_2 removal can be virtually complete, and the patient will remain nearly apneic in an atmosphere of pure oxygen obtained by a CPAP helmet; his/her will breathe just when his/her needs to speak or to cough.

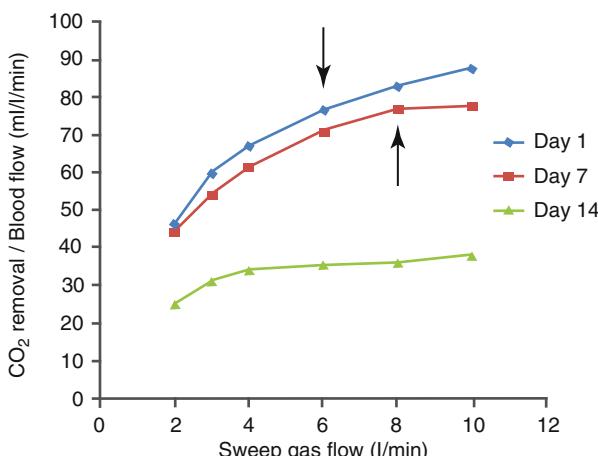


Fig. 24.2 Relationship between sweep gas flow (SGF) and extracorporeal CO_2 removal (expressed as ml/min per liter of blood flow) in a clinical case of awake vvECMO. Blood flow on days 1, 7, and 14 was 2.5, 2.7, and 4.2 l/min, respectively. Compared to day 1, the CO_2 removal function slightly deteriorated on day 7, while it greatly deteriorated on day 14. Oxygen desaturation (values not showed) associated with critical alveolar hypoventilation due to excessive extracorporeal CO_2 removal occurred at an SGF of 6 l/min on day 1 and 8 l/min on day 7 (arrows); it never occurred on day 14, due to the limited CO_2 removal even at high SGF

24.6.2 Adaptation to Changes in Extracorporeal Support Function

Once a good compensation of the failing respiratory function is achieved, the system may become unstable because of an imbalance between the extracorporeal support and the native respiratory function.

Thanks to its pump, vvECMO is typically more stable than an av pumpless respiratory support, during which the extracorporeal blood flow (that affects CO₂ removal, to a given extent) strongly depends on arterial blood pressure [11]. With an av pumpless support, blood flow and CO₂ removal can also be greatly affected by movements of the lower extremities, with increased resistance of the cannulas due to bending and position changes.

Although much more rarely, also during vvECMO blood flow can become unstable, due to bending of cannulas or tubes or to poor blood drainage because of hypovolemia. However, when cannulation and volemic status are adequate, the main technical factor requiring an adjustment of ECMO settings is represented by the progressive deterioration of the artificial lung function. In Fig. 24.2 it can be noted how, at any level of sweep gas flow, the CO₂ removal efficiency was much lower on day 14 than on ECMO start or on day 7; moreover, on day 14 no further increase of CO₂ removal could be obtained by increasing the gas flow above 4 l/min, indicating the need for oxygenator replacement. The progressive deterioration of the artificial lung may affect first CO₂ removal and only later oxygenation (Fig. 24.3). Up to a given extent, the deterioration of the extracorporeal CO₂ removal function can be compensated by increasing the ventilation of the artificial lung. Manual adjustment of ECMO gas flow to compensate for progressive deterioration is particularly important in the awake patient, who otherwise would react, thus becoming unstable.

24.6.3 Adaptation to Changes in Patient State

Modern ECMO systems are designed to be safe, simple, and stable, but not to adapt to changes in patient's needs.

Fever is a particularly challenging condition during awake ECMO. Except for the very-low-resistance Novalung® ILA®, ECMO circuits are combined with a temperature-regulated heat exchanger that effectively compensates the heat loss continuously taking place through the extracorporeal system. The heat exchanger may also display the power, expressed in watts, instantaneously applied in order to warm the blood at the set temperature.

In sedated patients on ECMO, a rise of internal body temperature above the heat exchanger set point (usually set at 37 °C) is rare, even when the heat exchanger is not provided with an active cooling function. When fever tends to rise, the heat exchanger decreases or even stops to heat the blood, and so the entire ECMO circuit becomes a passive cooler. Therefore, unless patient's thermogenesis is extremely high, in sedated patients on high-flow ECMO, fever may have little evidence: any

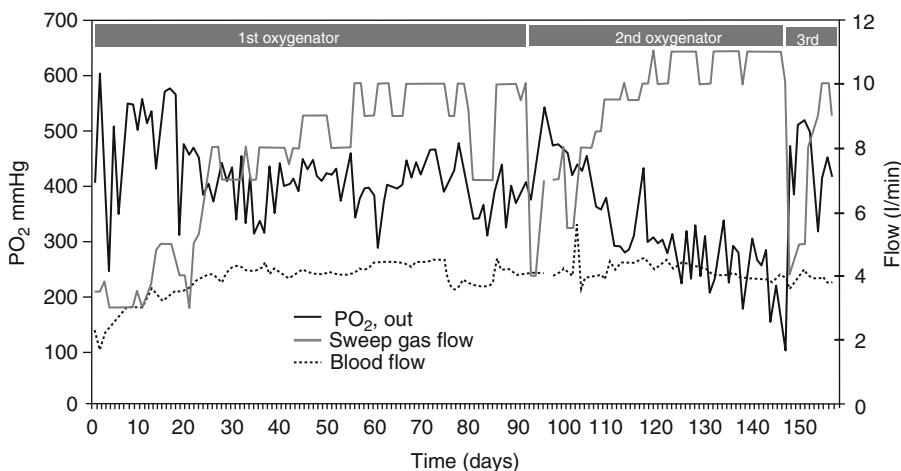


Fig. 24.3 Prolonged awake vvECMO. The first oxygenator was replaced after 90 days, when the oxygenation performance was still satisfactory (see PO_2 in blood leaving the oxygenator – PO_2 , out), while CO_2 removal had deteriorated, requiring a progressive increase of sweep gas flow (SGF) up to 10 l/min (corresponding to a progressive increase of extracorporeal ventilation/perfusion ratio from 1:1 to 1:2.5). With the second oxygenator, the slow deterioration involved simultaneously both CO_2 removal and oxygenation

potential increase of body temperature is prevented by extracorporeal circulation, while shivering may be blocked by sedation. Interestingly, information about this “not expressed fever” can be provided by the ECMO heat exchanger that will show that the set blood temperature (for instance, 37 °C) is achieved with zero or near-zero watts.

During awake ECMO the issue of fever is totally different compared to sedation, because the awake patient has much more power for fighting against the thermostatic action of the ECMO system. Typically, patients on awake ECMO react by strong shivering, which involves a major increase of oxygen consumption and tissue oxygen extraction, with relevant drop of venous oxygen saturation. In this framework, the consequent deterioration of oxygenation could be wrongly attributed to a malfunction of the vvECMO system (Fig. 24.4). Therefore, the typical picture of an awake patient on ECMO with an attack of fever includes shivering, respiratory distress with worsening of arterial blood gases, apparent worsening of the oxygen output from the oxygenator, no rise (or minimum rise) in body temperature, and “zero watts” on the display of the ECMO heat exchanger.

In such cases, a fast and relevant clinical improvement can be obtained by administering an antipyretic, by increasing the ventilation of the artificial lung, but above all by temporarily increasing the set point of the ECMO heat exchanger (from 37 to 38 °C or even more), aiming at a better coupling between artificial thermoregulation and patient’s thermoregulation. A kind of “artificial fever” thus matches the body’s attempt to rise its temperature, instead of opposing to that. Usually this simple

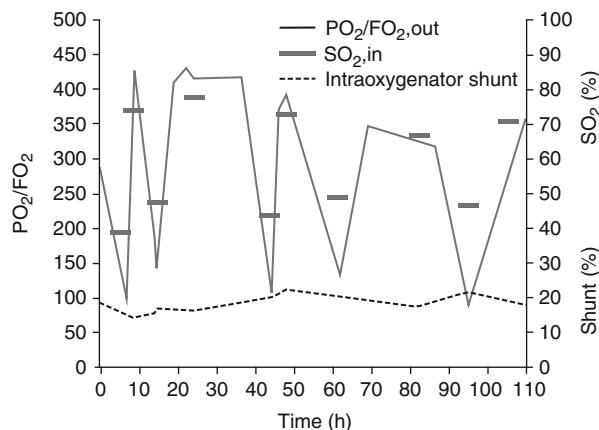


Fig. 24.4 Awake vvECMO with sepsis and “not expressed fever”: instability due to high oxygen consumption. Five events of apparent loss of performance by the oxygenator: the oxygen output, evaluated in terms of output blood PO_2 during ventilation with 100 % oxygen (PO_2/FO_2), considerably dropped. A complete analysis showed that, on the contrary, the oxygenator performance (evaluated in terms of intra-oxygenator shunt) was quite stable, while each event was marked by a significant drop of oxygen saturation of the venous blood entering the oxygenator (SO_2, in). During each event, the patient was shivering, while the internal body temperature was stable at 37 °C all the time

change stops shivering and thus greatly limits the increase in patient’s oxygen consumption and CO_2 production. After some hours, this “artificial fever” should be progressively reduced while checking patient’s tolerance.

24.6.4 Ventilatory Support

The ventilatory support of patients on awake ECMO ranges from simple oxygen therapy to NIV. As discussed above, the choice is wider when the oxygenating power of ECMO is large. On the contrary, when extracorporeal oxygenation is limited, it is necessary to maximally exploit the residual oxygenation function of the native lung by applying CPAP or NIV.

A positive pressure treatment with CPAP or NIV can be chosen also with the aim of preventing a progressive derecruitment of the lungs. Actually, also during awake ECMO as a bridge to lung transplantation, it is wise and recommendable to maintain the native lung open and working, if possible, while respecting its functional and mechanical limits and avoiding injuries due to mechanical ventilation.

Helmet CPAP [22] with active humidification is our preferred option for ventilatory support during awake ECMO. For a prolonged continuous application, helmet CPAP has less complications and is tolerated much better than mask CPAP or NIV. The good tightness that is typical of the helmet allows to maintain easily a high level of CPAP and/or a high oxygen concentration. High-flow humidified nasal oxygen is an interesting option whenever patients need to remove the helmet.

24.6.5 Circuit Replacement

The replacement of the ECMO circuit is more critical during awake treatments than in intubated patients. Patients on high-flow vvECMO have a particularly high risk for severe deterioration of oxygenation, as well as patients on vaECMO. It must be considered that, during the time of ECMO stop, a patient highly dependent on the extracorporeal support will suddenly feel like suffocating, if awake.

Therefore, circuit replacement must be performed at least under sedation and NIV. In some cases, temporary invasive ventilation can be considered. In rare cases, the replacement has been performed under hypothermia.

All the clinical staff must be well trained to perform a fast and smooth replacement, as well as ready to face the possible complications, including cardiac arrest. Maximum reduction of the time of ECMO stop is important; nonetheless, when restarting the bypass, a gradual progression in increasing the pump speed must be observed.

24.6.6 Psychological Issues

Compared to life support treatments delivered under sedation, awake ECMO may expose the patient to relevant psychological stress. Patients on awake ECMO share with their relatives the awareness that their own life depends on the ECMO machine as well as on the education and skill of the ICU staff. In bridge to lung transplantation, this is added to the fear that donor's organs may not be made available in time. Patients may differently express, or hide, their fear of dying, despair, and depression.

Patients can be relieved by family presence, psychological assistance, anxiolytics, and antidepressants. It is very important that the entire ICU staff gains patient trust.

24.7 Conclusion

By improving safety and ease of use, the latest ECMO technology allows to consider ECMO even before intubation in selected cases of lung failure. Up to now, bridge to lung transplantation has been the wider field of application of ECMO in non-intubated patients. Using ECMO in awake patients raises several specific issues that must be well known to warrant a successful clinical outcome.

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Stefania Crotti and Alfredo Lissoni

25.1 Introduction

Lung transplant (LTx) has now become a therapeutic tool for many end-stage respiratory failures. In the last 10 years, the number of lung transplants has doubled, and the 1-year survival rate has significantly increased from 75 % to more than 80 % [1]. However, the mortality rate of patients on waiting lists for lung transplant is still high, due to the scarcity of lung donors and the difficulty in managing patients with end-stage respiratory failure.

The progression of respiratory disease can cause different clinical scenarios, ranging from hypercapnia alone to both hypercapnia and hypoxia, with eventual associated pulmonary hypertension. In some cases, medical therapy is unable to control the worsening of respiratory failure, and an artificial respiratory support is needed until a suitable organ becomes available.

Until a few years ago, when the noninvasive ventilation (NIV) failed, the invasive mechanical ventilation (IMV) was the only artificial respiratory support for bridging patients to lung transplant. The mortality rate of the patients awaiting LTx on mechanical ventilation varies from 13 % [2] up to 90 % [3]. These data reflect the extreme variability of the pathophysiologic and mechanic characteristics of the lung affected by the “transplantable” disease. The invasive mechanical ventilation of the emphysematous lung increases the risk of pneumothorax, which could lead to a high-flow air fistula, thus making the mechanical ventilation itself ineffective. Furthermore, positive pressure IMV can worsen a severe case of pulmonary hypertension. Lastly, patients with end-stage respiratory failure (i.e., cystic fibrosis, CF) are particularly exposed to the ventilator-induced lung injury (VILI) and the

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ventilator-associated pneumonia (VAP) due to the pulmonary chronic inflammation caused by the recurrent infections [4].

Although the use of the extracorporeal respiratory support as bridge to lung transplant was first reported more than 30 years ago [5], the increasing number of transplant centers that have started ECMO programs to bridge critically ill patients to lung transplant is only recent, thanks to the technological improvements of the extracorporeal systems.

The ECMO support as bridge to lung transplant can provide the following:

1. Extending the bridge option to the patient with a high risk of complications related to IMV (i.e., bullous emphysema and severe pulmonary hypertension)
2. Decreasing VILI when associated to IMV
3. Avoiding the risk of VAP when patient is maintained conscious and not intubated
4. Reducing respiratory distress in conscious patients both on NIV or IMV

Nevertheless, the bridge to lung transplant still remains a controversial topic. The main reason is that the patients who need an artificial respiratory support have a higher perioperative risk of death. Thus, considering the scarcity of the lung donors, the use of organs in patients with lower postoperative survival could be considered a waste of resources. However, health economists have proposed the concept of “benefit of survival” to improve the effectiveness of health budgets [6]. This concept introduces the idea that, in a contest of scarcity of resources, these resources should be reserved to patients with higher survival benefit. This idea has been also applied to organ donations. The lung allocation score (LAS) has been introduced in the United States in 2005 [7]. According to this score system, the organ is assigned to the recipient with the higher predicted survival at 1 year, hence balancing the risk of death on waiting list with the survival after the transplant. However, larger and long-term survival studies are needed to determine if the LAS system improves overall allocation and survival for patients interested in lung transplant. In other countries, such as Italy, critically ill patients are prioritized through urgent lists.

Although patients undergoing ECMO bridging to LTx have to be considered critically ill, recent larger case series (Table 25.1) report a promising short- and medium-term survival, which justifies the increasing use of the ECMO tool by many centers.

25.2 Indications, Timing, and Patient Selection

The main indications for the ECMO bridging to lung transplant include all the irreversible end-stage respiratory diseases, which have a rapid worsening of the respiratory function, as well as severe pulmonary hypertension with right-sided ventricular failure.

So far, there is no evidence regarding the correct timing of the artificial respiratory support. Some centers start the ECMO bridging when the clinical condition deteriorates to the point that the patient’s life expectancy could be considered less than 24–48 h without intubation and/or extracorporeal support.

Careful patient selection is needed to maximize the results of ECMO bridging and to avoid a waste of viable donor lungs. In our center we have applied ECMO bridging in LTx candidates in whom respiratory failure is the sole relevant organ

Table 25.1 Experiences of the use of ECMO as bridge to LTx (series with more than ten patients)

Reference	Year	No. of patients	Bridge duration (days)	Type of ECMO	Successful bridge (%)	1-year survival (%)
Fischer et al. [8]	2006	12	15±8 (4–32)	AV	83	80
Cypel et al. [9]	2010	10	5 (1–25)	VA (3), VV (2), AV (4), PA-LA (4)	100	70
Ricci et al. [10]	2010	12	13.5±14.2 (4–48)	AV (6), Decap (6)	25	NA
Hammänen et al. [11]	2011	16	16.8±19.2 (1–59)	VV, VA	81	92
Bermudez et al. [12]	2011	17	3.2 (1–49)	VV (8), VA (9)	NA	74
Fuehner et al. [13]	2012	26	9 (1–45)	VV (14), VA (12)	77	80 (6 months)
Lang et al. [14]	2012	34	4.5 (1–63)	VV (18), VA (14), AV (1), comb (4)	76	60
Javidar et al. [15]	2012	18	11.5 (6–18)	VV (13), VA (5)	72	100 (3 months)
Shafii et al. [16]	2012	19	6.5 (1–16)	VV (11), VA (8)	74	75
Toyoda et al. [17]	2012	31	7.1±10.1 (0.1–46)	VV (15), VA (9), 7 NA	77	74
Hoopes et al. [18]	2013	31	11 (2–53)	VV (13), VA (12) PA-LA (3), comb (4)	NA	92
Crotti et al. [19]	2013	25	24±31 (1–157)	VV (19), VA (2), AV (4)	68	76

AV arteriovenous, VV venovenous, VA venoarterial, PA-LA pulmonary atrium-left atrium, *comb* combination

failure (aside from right-sided heart failure) and in whom no exclusion criterion for LTx or ECMO is present.

The most common behavior is to use this therapeutic option for patients: already candidates for lung transplant, young, free from other organ failures, and with a good expectancy of physical recovery after transplant. This is because factors, such as age, organ dysfunction, some infections, and physical status, are risks for postoperative death, even for patients on the standard list [1]. It is worth noting that the postoperative survival of patients is affected by the recipient's age. In fact recipients older than 55 have a significantly higher risk of death at 1 year after transplant [1].

The coexistence of other organ dysfunctions alongside the end-stage respiratory failure and/or pulmonary hypertension decreases the 1-year survival after LTx. Particularly the need of hemofiltration and the use of inotropic drugs in the perioperative period are risk factors for the 1-year mortality [1].

Septic shock is a contraindication for lung transplants, whereas the presence of leukocytosis and fever in the immediate preoperative period slightly increases the

risk of death for postoperative sepsis [20]. In CF patients, the pre-transplant pulmonary colonization with *Burkholderia cepacia* genomovar III increases postoperative mortality, whereas the colonization with other *B. cepacia* strains, or multi- or pan-resistant *Pseudomonas aeruginosa*, or methicillin-resistant *Staphylococcus aureus*, or *Aspergillus fumigatus*, does not affect postoperative survival [20].

Investigations of muscle function in lung transplant recipients reveal decreased muscle mass and strength with a persistent limitation in exercise capacity at 1 year after LTx. Pre-existing peripheral muscle dysfunction in chronic lung disease is one of the determinants of the postoperative impairment in physical status, suggesting a need for physical therapy to optimize muscle strength and functional capacity during the pre-transplant period [21].

25.3 ECMO Configuration

Deciding the type of extracorporeal support must take into account the characteristics of the respiratory failure, the presence of pulmonary hypertension, and the concomitant right-sided heart failure. The ECMO approach and the specific device chosen will fit with the clinical patient's condition (Fig. 25.1).

Most end-stage respiratory diseases, requiring lung transplant as a unique therapeutic option, lead to a mainly hypercapnic respiratory failure. When the noninvasive trial fails, the extracorporeal support becomes a valid option to bridge these

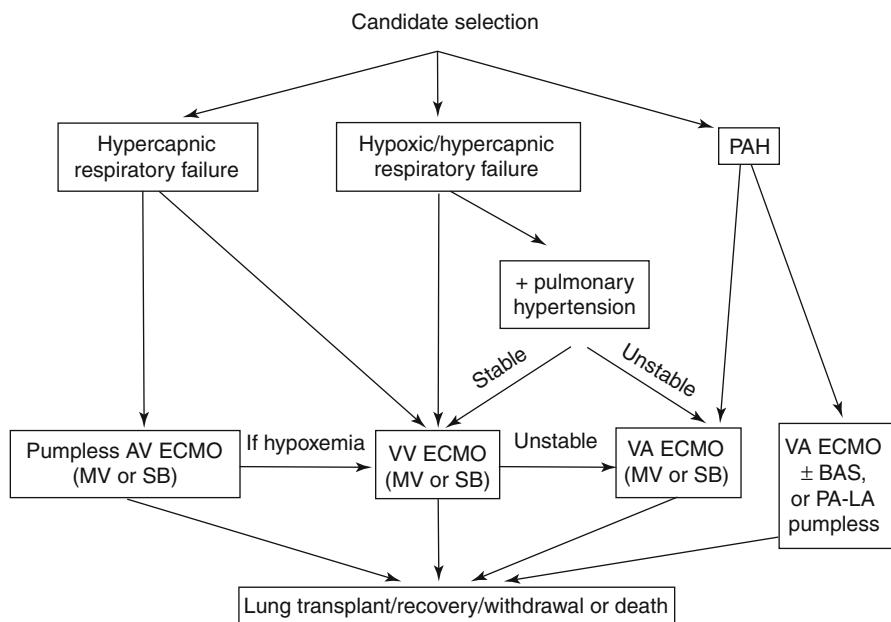


Fig. 25.1 Algorithm for selection of ECMO support configuration

patients to LTx. In the hypercapnic patients, the two configurations most often used are the pumpless arteriovenous (AV) and the venovenous VV ECMO.

The pumpless arteriovenous (AV) approach has been recently utilized successfully. The first report is by Fisher et al. who described the use of the “novel pumpless device” in 12 patients between 2003 and 2005 [8]. They reported a very successful bridge to LTx (10 of 12 patients underwent a transplant) and an 80 % 1-year survival. Other groups experienced the low blood flow – CO₂ removal devices reporting different successful rate. Ricci et al. described 12 patients treated with pumpless AV or decap navigation system Decap [10]. They were able to reverse the respiratory acidosis, but 8 of 12 patients died prior to transplant. Cypel et al. recently published four patients successfully bridged to LTx with the AV mode and another four patients that required a conversion to a VV or venoarterial VA ECMO during the bridging period [9].

In the AV ECMO setting, the blood is driven through the circuit by the difference between the femoral arterial pressure and the venous reinfusion pressure. This requires an adequate patient’s mean arterial pressure. Moreover, in AV mode the ECMO blood flow cannot be actively changed (maximum value of 1–1.5 L/min), limiting the extracorporeal oxygen supply. If the patient’s oxygenation drops during the bridge period, a switch to a VV configuration becomes necessary, with possible bleeding problems at the arterial cannula removal site. In AV mode, heart performance must be good enough to increase the patient’s cardiac output as requested by the high-flow “fistula”, as the AV ECMO could be considered. Nevertheless, AV mode offers an optimum and effective CO₂ removal that can be titrated by changing the sweep gas flow from a minimum level up to 12 L/min.

Some end-stage respiratory failure could be both hypercapnic and hypoxic. The VV configuration permits controlling respiratory acidosis through an adequate CO₂ removal and provides oxygen supply by varying the ECMO blood flow up to 4–5 L/min. If recirculation is minimized, even in the presence of severe hypoxic disease, the VV mode could be feasible in managing the patients until a suitable organ becomes available. Most of the transplant centers have recently increased the use of this approach for all the patients without right-sided heart failure. Up until 2007, only single-center case reports had been published [22]. In the last 4–5 years, many centers around the world have reported an increased experience [8–19]. As shown in Table 25.1, in which the case series of more than ten patients are listed, the VV approach is the more frequently used in each center. The VV configuration could also support blood gasses during the intraoperative management of the patient, and, whenever possible, it should be preferred to a central VA bypass. This offers some advantages, such as less need of intraoperative anticoagulation, simpler technical management, and better evaluation of graft performance after LTx.

Moreover, the VV configuration could be chosen to bridge to LTx hypercapnic and hypoxic patients even in the presence of secondary moderate to severe pulmonary hypertension, if they are hemodynamically stable without signs of right-sided heart failure. In fact, as previously described in 11 severe ARDS patients, the increase of the mixed venous oxygen tension reduces the pulmonary vascular resistance as a consequence of the decreasing hypoxic pulmonary vasoconstriction [23]. Furthermore,

the normalization of the arterial carbon dioxide tension and consequently of the pH could reduce the pulmonary pressure itself. We observed the decrease of the pulmonary vascular resistance in many ARDS patients just after the ECMO onset, and we recently report a case of a bridge to LTx with VV ECMO in severe pulmonary hypertension secondary to acute on chronic respiratory failure Oral communication at Euro Elso meeting Stockholm 2013.

A different clinical scenario is the primary pulmonary arterial hypertension (PAH). In these patients, the pathophysiology of the underlying disease is difficult to be reversed and, in the end-stage of the disease, often leads to a severe right-sided ventricular failure. The ECMO configuration used in this condition is the VA mode, which can offer a complete support of gas exchange and hemodynamics. If peripheral VA approach is performed, the upper body and the coronary vessels could be poorly oxygenated (Harlequin syndrome). The improvement of the upper body oxygenation can be achieved by the insertion of an additional cannula into the internal jugular vein, modifying the circuit in the hybrid VAV [24]. The VA ECMO is the former approach described to bridge patients to lung transplantation even in the exclusively respiratory disease. Now, this support is usually reserved to the cardiac-respiratory failure. In sheep suffering from respiratory failure and right ventricle dysfunction, Camboni D et al. have recently described the use of VV ECMO associated to the balloon atrial septostomy (BAS) and so creating a right to left shunt and then unloading the right ventricle [25]. However, the right to left shunt drives an amount of desaturated blood in the left side, and this could worsen the hypoxia. A recent approach described by some authors in few patients is pulmonary artery to left atrium (PA-LA) configuration [26]. This is a pumpless system, which takes advantage of the higher PA pressure to drive blood through the artificial lung (Novalung^R) into the left circulation. This configuration needs a sternotomy and a central cannulation to be performed.

The cannulation site often depends on the ECMO configuration chosen and for each configuration on the center's experience and preference.

The pumpless AV ECMO is always performed with a peripheral cannulation draining from the femoral artery and reinfusing into the femoral vein. Instead, VV configuration can be obtain with four different cannulation approaches. The femoro-femoral approach, which is our center's preference, is safe, easy to perform (even in the "awake" patients) (Fig. 25.2), but does not permit patients standing out of bed and their ambulation. The femoro-jugular cannulation has been shown to be more effective than the reverse approach (i.e., jugular-femoral), reaching higher venous oxygen saturation at the same blood flow [27]. The use of the double-lumen cannula has recently been implemented thanks to the technological improvement of the cannula's manufacture and its use in the "awake" patient [28]. This cannulation type follows the sedation and intubation of the patient; some adverse events have been recently described during the cannula insertion; the correct position is difficult to be achieved and needs frequent echocardiographic or fluoroscopic daily checks. However, with this cannulation patients can stand up, ambulate, and follow an active physical therapy.

The VA ECMO can be performed with a peripheral or a central cannulation. Some centers in the peripheral cannulation routinely insert additional distal perfusion catheter in place to prevent leg ischemia. The central cannulation, which



Fig. 25.2 Awake ECMO as bridge to lung transplant

follows a sternotomy, is the more frequent intraoperative approach, and it is required when the PA to LA configuration is performed.

25.4 Patient Management

The main goal in patient management during ECMO as bridge to lung transplant is to avoid the development of further organ dysfunctions aside from respiratory failure that increases morbidity and mortality during bridge and after transplant. We recently reported a retrospective on two Italian centers and their study showing the effects of the duration of the extracorporeal bridge to lung transplant [19]. In this study, we observed that the patients who awaited organ allocation less than 2 weeks had a higher survival and a better postoperative course compared to the patients with longer bridge duration. This was related to the clinical impairment during the bridge course as shown by the difference in the pre-transplant SOFA score, higher in the group that awaited the organ allocation longer. And so, the objective to decrease the ECMO bridge duration justifies the use of high-priority lists for these critically ill patients.

In mechanically ventilated patients, the protective ventilation of the native lungs, although they may not recover their function, could reduce adverse events such as right cardiac dysfunction, sepsis, and multiple organ failure. However, mechanical ventilation per se can worsen the patient's clinical condition. The Hannover group has recently described the "awake" ECMO approach, maintaining the patient non-intubated, on spontaneous breathing [13]. This "awake" ECMO strategy reduces the

well-known drawbacks related to sedation and mechanical ventilation. Furthermore, “awake” patients can follow an active physical therapy in order to reduce neuromuscular dysfunction. This approach can be used regardless of the underlying disease and the ECMO configuration chosen, as reported by the same group during AV or VV approach and also in the VA ECMO-supported patients [13, 29]. In this ECMO setting, attention has to be made to titrate the CO₂ removal, both seeking respiratory distress relief and avoiding pulmonary hypoventilation, which can occur by increasing the ECMO CO₂ removal too much. The use of the “awake” strategy could be more complicated in the CF patients due to the huge amount of pulmonary secretions that are more difficult to be cleared if the patient reduces his own ventilation as well as the ability to cough. The need to stand out of bed and ambulate patients is better satisfied by the use of the double-lumen cannula, recently implemented in some transplant centers.

If the other organ functions deteriorate, intensive care is needed for organ support as hemofiltration for renal dysfunction or inotropic drugs for cardiovascular failure. When the patient deteriorates during the ECMO bridge, support withdrawal has to be taken into account and the patient can be deemed unfit for transplant.

25.5 Outcome

Technological advances allowing a safer application of the ECMO circuits, as well as changes in choosing the bridge configuration, involving the widest use of the VV support (instead of the more invasive and complicated VA approach), have lead to considering ECMO as a valid tool to bridge the critically ill patients to lung transplant. The data so far available on postoperative survival, in some experienced centers quite equal to the patients on the standard waiting lists, are satisfactory enough to justify its use. The main effort in increasing bridge success and the postoperative course is to improve the preoperative clinical condition through the physical exercise and the maintenance of multiple organ function integrity. The “awake” strategy seems to obtain better results in terms of postoperative morbidity, but not enough data on differences in survival rate are yet available. Many centers believe in this strategy, following an active physical therapy in awake and ambulatory patients.

A wider experience, a larger case series, and long-term follow-ups are needed to confirm the use of the ECMO to bridge critically ill patients to lifesaving transplants. Furthermore, a careful evaluation of each individual patient is necessary to correctly choose candidates for lung organ allocation, so as to avoid a waste of very scarce resources.

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26.1 Introduction

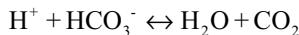
In 1952, the outbreak of poliomyelitis in Copenhagen recalls the first clinical scenario in which positive pressure mechanical ventilation (MV) was extensively applied to patients with acute respiratory failure. MV was able to restore the balance between weak respiratory muscles and inspiratory workload [1]. Paradoxically, depending on the impairment of respiratory system mechanics, the ventilator setting, per se, may cause macroscopic and microscopic lung injury, negatively affecting patient outcome [2, 3].

Thereafter—from the theoretical consideration that resting the lung could be the optimal solution to avoid ventilator-induced lung injury—finding a non-ventilatory strategy consisting of an extracorporeal support therapy that is able to clear CO₂ and ensure oxygenation is needed. In fact, there are different extracorporeal life support techniques (ECLS) ranging from low blood flow extracorporeal membrane oxygenation (low-flow ECMO) for extracorporeal CO₂ removal up to full high flow for oxygenation support (high-flow ECMO). In addition, less invasive systems designed only for extracorporeal CO₂ removal (ECCO₂R) have been developed. The objectives of this chapter are to review current concepts of low-flow ECMO and ECCO₂R systems—removing only carbon dioxide, with little to no impact on oxygenation—and provide the rationale for their application in patients with ARDS and COPD and thoracic surgery candidates and for its use as bridge to lung transplantation.

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26.2 Physiology of CO₂ Removal During Extracorporeal Support

CO₂ produced within aerobic cellular respiration is transported from tissues to the lungs through blood in three main ways: 90 % of the total CO₂ is conveyed as bicarbonate ion (HCO₃⁻) that originates both from carbonic acid dissociation and CO₂ hydration according to the following equation:



The remaining 10 % is transported as CO₂ freely dissolved in blood (5 %) and as carbaminic compounds, arising from the interaction of CO₂ and the aminic groups of circulating proteins, like hemoglobin.

Under physiological conditions, the amount of CO₂ produced during systemic metabolism (VCO₂) is 200 ml/min, which can increase to a value of 30 % higher in pathological condition. As a consequence, the concentration of CO₂ in arterial blood is about 480 ml/l, and in mixed venous blood it rises 10 % to a value of 520 ml/l, corresponding to a partial pressure of CO₂ (PCO₂) of 40 and 45 mmHg, respectively. It is possible to argue that 1 l of blood contains two times the amount of CO₂ produced in the whole body per minute. Theoretically, it is possible to remove 250 ml/min of CO₂ by the filtration of 500 ml/min of blood during extracorporeal support depending on specific efficiency of the systems. In light of these considerations, CO₂ removal may be achieved with blood flow rate lower than 1 l/min and ventilating the membrane lung with a fresh gas flow (sweep gas) to maintain the CO₂ gradient across the artificial lung [4, 5].

26.3 Clinical Applications of Low-Flow ECMO and ECCO₂R Systems

Currently, extracorporeal life therapies are indicated for the temporary support of the pulmonary function to gain time waiting for full recovery of organ function or as a bridge to organ transplantation. In the following section, several diseases, in which low-flow ECMO and ECCO₂R systems are used as therapeutic interventions, will be discussed (Table 26.1).

26.4 Acute Respiratory Distress Syndrome (ARDS)

In patients with ARDS, extracorporeal life support techniques are currently applied for two main reasons: first, as rescue therapy for life-threatening hypoxemia that is refractory to conventional mechanical ventilation and, second, as adjunctive therapy to conventional mechanical ventilation to allow ultra-protective ventilation that minimizes VILI, limiting end-inspiratory lung stretch. As previously mentioned, these two applications of ECLS are coupled with different complexities and

Table 26.1 Clinical studies that evaluate the efficacy of ECMO and ECCO₂R systems in different diseases

Author	Type of study	Baseline	MV settings After extracorporeal support	ECCO ₂ R settings		Heparin	Outcome	Complications
				ECCO ₂ R settings	Heparin			
A-RDS								
Gattinoni et al. [6] (n=3)	Case report	RR=1.6–22/min (minute ventilation 14–25 l/min)	RR=3/min (minute ventilation 0.7–1.5 l/min)	VV ECMO-LFPPV Blood flow 1.3 l/min Sweep gas 16 l/min	Single bolus+CI	A, B		
Gattinoni [7] (n=43)	Prospective interventional		PIP<35–45 cmH ₂ O PEEP 15–25 cmH ₂ O RR=3–5/min	VV ECMO-LFPPV Blood flow 1 l/min Sweep gas 15 l/min	Single bolus	A, B	a, b	
Brunet et al. [8] (n=23)	Prospective interventional	VT=720±150 ml PIP=51±9 cmH ₂ O PEEP=13±2 cmH ₂ O RR=1.6–24/min	VT=290±35 ml PIP=36±6 cmH ₂ O RR=4/min	VV ECMO-LFPPV Single bolus+CI	A, B	a, b		
Morris et al. [9] (n=40)	RCT	C arm (n=19): conventional Int arm (n=21) VT=8.9±0.6 ml/kg PIP=55±3 cmH ₂ O	Int arm (n=19) Pressure control inverse ratio ventilation	VV ECMO-LFPPV CI Blood Flow 2.4 l/min	No benefit in a, b terms of survival, hospital, and ICU length of stay			
Bein et al.* [10] (n=90)	Retrospective	VT=430 (360–450) ml PIP=38 (35–40) cmH ₂ O RR=27 (21–43)/min	VT=380 (320–470) ml PIP=35 (31–39) cmH ₂ O RR=23(17–39)/min	A-V ECCO ₂ R pumpless Blood flow 1.9–2.5 l/min	Single bolus+CI	A, B	c	
Florhinger et al. [11] (n=159)	Prospective observational	VT=453±134 ml PIP=37.7±6.3 cmH ₂ O RR=37±15/min	VT=402±144 ml PIP=34.5±7.2 cmH ₂ O RR=29±17/min	A-V ECCO ₂ R pumpless Blood flow 1.9–2.1 l/min Sweep gas 6–13 l/min	CI-coated system	A	c, d	

(continued)

Table 26.1 (continued)

Chronic obstructive pulmonary disease (COPD)					
Author	Type of study	MV settings	ECCO ₂ R settings	Heparin	Outcome
Burki et al. [14] (n=20)	Prospective observational	Noninvasive MV at risk for intubation and invasive MV after failing weaning trial	VV ECCO ₂ R Blood flow 0.43±74 l/min	Single bolus+CI	A, thrombocytopenia Low rate of noninvasive MV failure
Thoracic surgery					
Author	Clinical setting	Type of study	MV settings	ECCO ₂ R settings	Heparin
Hommel et al. [15] (n=4)	Postsurgical bronchial fistulae with ARDS	Case report	VT<4 ml/kg PBW RR=23–22/min PIP<30 cmH ₂ O	A-V ECCO ₂ R pumpless	CI
Wiebe et al. [16] (n=10)	Apneic oxygenation during thoracic surgery	Observational	Apneic oxygenation	A-V ECCO ₂ R Blood flow 1.58±0.3 l/min	A, B Hypothermia
				Single bolus + CI	
				Sweep gas	
				6–12 l/min	

Bridge to lung transplantation		Author	Type of study	MV settings	ECCO₂R settings	Heparin	Outcome	Complications
Ricci et al. [17] (<i>n</i> =12)	Observational			A-V ECCO ₂ R (<i>n</i> =6)	Single bolus+CL		A, B	
Fuehner et al.* [18] (<i>n</i> =60)	Retrospective	MV arm (<i>n</i> =34) conventional MV settings ECMO arm (<i>n</i> =26) in awake patients	Int arm (<i>n</i> =26) VV ECMO group Blood flow 2.8(2.3–3.8) l/min Sweep gas 4.0(3.0–5.5) l/min [VA ECMO group Blood flow 3.3(3.3–4.1) l/min Sweep gas 3.3(2.5–4.0) l/min]	VV-ECCO ₂ R (<i>n</i> =6) Single bolus+CL		ECMO was effective as bridge	a, b, e, sepsis-like syndrome multiorgan failure and need of renal replacement therapy	

Abbreviations: A Improvement in CO₂ removal in patients treated with ECCO₂R, a Hemorrhage—minor bleeding, B Improvement in ventilatory management, allowing protective MV thus reducing risk of VILI in patients treated with ECCO₂R, b Hemorrhage—major bleeding, C Improvement in ventilator-free days (VFD) at 60 days in patients with PaO₂/FiO₂ <150 in patients treated with ECCO₂R, c Complications related to ECCO₂R device such as plasma leak or circuit clotting, C arm Control arm, CI Continuous infusion, CO Cardiac output, d Lower limb ischemia, e Hemodynamic impairment, F_{flow} Blood flow through the ECCO₂R circuit, Int arm Interventional arm, MV Minute ventilation (l/min), P_{max} Maximum peak pressure allowed, PEEP Positive end-expiratory pressure, PIP Peak inspiratory pressure, RCT Randomized controlled trial, RR Respiratory rate, VILI Ventilator-induced lung injury, V_T Tidal volume expressed in ml or in ml/kg of predicted body weight

*Values are expressed as median (interquartile range)

invasiveness of ECLS apparatus. In fact, high blood flow (3–6 l/min) ECMO provides full oxygenation and CO₂ removal in severe ARDS patients with life-threatening hypoxemia. On the other hand, low blood flow (0.4–1 l/min) extracorporeal CO₂ removal (ECCO₂ R) apparatus removes all CO₂ produced by metabolism with minimal effect on oxygenation. In the following paragraphs, the current application of ECCO₂ R in patients with ARDS will be reviewed. The reader is referred to other chapters for high-flow ECMO in ARDS.

Seminal animal observations which showed that extracorporeal CO₂ removal was able to progressively reduce the respiratory drive [19] were the rationale to apply an ultra-protective ventilation strategy to humans, with the objective of keeping the lung at rest and avoiding the deleterious consequences of mechanical ventilation. In 1980, Gattinoni et al. described a small series of three patients in whom ECMO with a blood flow of around 1.3 l/min reduced the needs of inspiratory flow from 15 to 20 l/min to only 0.7–1.5 l/min, thus avoiding lung overdistension and barotrauma [6]. Six years later, the same authors showed convincing evidence that low-flow ECMO was a feasible and safe adjunctive therapy to conventional mechanical ventilation that was confined to merely support oxygenation [7]. In fact, 43 patients with early (1 week) and late (2–3 weeks) ARDS were treated with a veno-venous low-flow ECMO as last therapy after they failed conventional mechanical ventilation and other rescue therapies as high-frequency jet ventilation and inverse ratio ventilation. In particular, normal PaCO₂ values, a blood flow of 20–30 % of cardiac output on ECMO, a sweep gas of 15 l/min, and only five positive pressure limited breaths at 35–45 cmH₂O were obtained. Oxygenation was completely dissociated from CO₂ clearance; in fact, it was achieved through an apneic oxygenation that consisted of an oxygen flow rate of 2–3 l/min delivered at the level of the carina and PEEP similar to the value of mean airway pressure before the beginning of bypass. These patients had a mortality of 52.1 %, and this rate was lower than a reported value of 80 % in a previous NIH trial [7]. Of note, conflicting results of the above mentioned studies could be explained by the fact that despite patients having similar baseline characteristics, patients in the NIH trial were treated with artero-venous bypass and, more importantly, with full conventional mechanical ventilation that did not prevent barotrauma and VILI.

Moreover, these results were confirmed in a subsequent observational study of 23 patients with severe ARDS [8]. In this study, Brunet and colleagues reported a mortality rate of 52 % in patients with severe ARDS who were treated with low-flow ECMO and 5 breaths of conventional MV. The ECLS strategy reduced PaCO₂ from 56 to 41 mmHg ($p < 0.0001$) and tidal volume from 730 to 284 ml. Of note, four of 23 patients died during ECMO because of major bleeding complications [8]. In the same period, Morris and colleagues performed a single-center RCT, in which 40 patients with severe ARDS were randomized to receive conventional mechanical ventilation or inverse ratio ventilation (IPRV) and ECMO. No significant difference in survival (42 % conventional vs. 32 % ECMO group) was demonstrated between the two arms of study [9].

Despite the disappointing results of the two RCTs, the H1N1 influenza pandemic in 2009 dramatically prompted physicians to support young patients with severe

ARDS by viral pneumonia with ECMO. However, there has been a growing interest to look for simpler and less invasive ECCO₂R devices to assist conventional MV in order to minimize VILI without all of the risks associated with ECMO.

Toward this end, two new devices, pumpless extracorporeal lung assist (PECLA) (iLA Membrane Ventilator, Novalung GmbH, Hechingen, Germany) and Decap (Hemodec, Salerno, Italy), have been proposed. Novalung is a low-resistance A-V bypass (of approximately 15 mmHg at 2.5 l/min blood flow) with a diffusion membrane of poly-4-methyl-1-penten (surface of 1.3 m²), through which an oxygen flow of 1–12 l/min can be administered. It requires relatively small cannulae (15–19 F arterial and 17–19 F venous) and a priming volume of 200 ml of crystalloids.

Florhinger and colleagues published their 10-year experience using Novalung as a life-support device for patients with acute respiratory failure. In total, 159 patients were treated for 7.0 ± 6.2 days and 70 % of them had acute respiratory failure. Both PaO₂ (from 72 ± 37 mmHg to 203 ± 61 mmHg) and PaCO₂ (from 67 ± 24 mmHg to 39 ± 17 mmHg) improved at the end of treatment with a significant reduction of minute ventilation (from 13.8 ± 4.8 L/min to 9.8 ± 4.8 l/min) [11]. These data established Novalung as a reliable method of supporting ARDS patients. These results were confirmed in a retrospective study of 92 patients with ARDS in whom hypoxia and hypercapnia were promptly corrected; however, lower limb ischemia was reported in 24 % of cases [10]. More recently, in a multicenter RCT involving 10 hospitals, the same authors evaluated whether a VT of 3 ml/kg PBW enhances lung protection. In the treatment arm, patients with ARDS were ventilated with a VT of 3 ml/kg and PECLA support to obviate respiratory acidosis. In the control arm, patients were ventilated according to ARDSnet strategy (6 ml/kg PBW) without an extracorporeal device. The primary outcome—ventilator-free days at 30 and 60 days—was not different between the study groups. Unfortunately, the trial was stopped after 3 years, after 79 out of 106 patients were enrolled, as previously planned. However, a post hoc analysis showed that patients with severe hypoxemia (PaO₂/FiO₂ < 150) had improved ventilator-free days compared to controls [13].

A minimally invasive system that removes CO₂, Decap, has been proposed as an efficacious system that provides ultra-protective mechanical ventilation [12]. It consists of a modification of the continuous VV hemodialysis machine. Access is accomplished through a single double-lumen catheter inserted in the femoral vein. Blood flow is via a nonocclusive roller pump. Blood circulates through a membrane oxygenator (total membrane surface is 0.33 m²) then through a hemofilter. The ultrafiltrate from the hemofilter is recirculated into the pre-gas exchanger blood, increasing CO₂ removal. In an observational study, Terragni and colleagues demonstrated that Decap treatment associated with ultra-protective mechanical ventilation (VT < 6 ml/kg PBW) may mitigate VILI. In 32 patients with ARDS ventilated with a VT of 6 ml/kg PBW, those with plateau pressures between 28 and 30 cmH₂O had their VT reduced to achieve plateau pressures between 25 and 28 cmH₂O. Respiratory acidosis (pH ≤ 7.25) derived from VT reduction was managed with Decap for at least 72 h. Alternatively, patients who already had plateau pressures between 25 and 28 cmH₂O continued to receive protective MV (VT of 6 ml/kg PBW). In the ECCO₂R group (ten patients), PaCO₂ (mean 50 mmHg) and pH (mean 7.32) were normalized,

and VT was reduced from 6 to 4 ml/kg PBW, and plateau pressure decreased from 29 to 25 cmH₂O ($p < 0.001$). Moreover, there was a significant reduction in the percentage of lung hyperinflation in the treatment group at 72 h, as demonstrated by CT scan and pulmonary cytokines ($p < 0.01$). No patient-related complications occurred in patients receiving Decap treatment [12]. Of note, Zanella and colleagues showed a new method to improve the CO₂ removal in the system mentioned above. In six pigs, blood acidification through continuous infusion of 0.5 N lactic acid increased the CO₂ removal capacity of the membrane lung up to 70 % [20].

26.5 Chronic Obstructive Pulmonary Disease (COPD)

COPD represents the third cause of death in the USA [21], and hypercapnic respiratory failure worsens prognosis and increases mortality [22, 23].

Noninvasive positive pressure ventilation (NIPPV) is able to reduce the number of patients requiring intubation, and it represents the standard of treatment of patients with acute exacerbation of COPD [24]. However, NIPPV fails in 25–50 % of COPD patients who still require invasive positive pressure ventilation (IPPV) [25] with a poor prognosis in terms of hospital survival [26].

During acute exacerbation of COPD, dynamic hyperinflation (due to shorter expiratory time) and expiratory flow limitations (due to compression of small airways) increase the value of intrinsic PEEP (PEEPi), thus worsening respiratory acidosis and work of breathing.

As previously mentioned, the ECCO₂R techniques were applied first in patients with hypoxic respiratory failure, but their role in hypercapnic respiratory failure has not been properly addressed.

In a proof of concept study, Burki et al. examined the application of a novel, single venous catheter ECCO₂R system in patients with acute exacerbation of COPD. The authors demonstrated that this single-catheter, low-flow ECCO₂R system was able to partially remove CO₂, improving some aspects of this complicated disease. The study involved 6 ICUs (1 in India and 5 in Germany), and 20 hypercapnic patients with COPD were treated with ECCO₂R in three different ways. In the first group (7 patients), patients failing NIV were treated with a minimally invasive extracorporeal CO₂ removal system with the aim of avoiding tracheal intubation. In the second group (2 patients), patients who could not be weaned from NIV were treated. In the third group (11 patients), patients who underwent invasive ventilation received ECCO₂R to improve the process of liberation from mechanical ventilation. Blood flow through the system ranged between 117 and 587 ml/min (mean \pm SD of 430.5 ± 73.7 ml/min) with an elimination of CO₂ ranging between 14 and 121 ml/min (mean \pm SD of 82.0 ± 16.3 ml/min). The rate of complications was similar to those observed with central venous catheterization. Of interest, this minimally invasive ECCO₂R strategy prevented intubation in all patients who were failing NIV, serving as feasible adjunctive therapy during acute exacerbation of COPD [14].

Similar strategies are the subject of an ongoing observational phase 2 Italian study (Extracorporeal CO₂ Removal in COPD Exacerbation—DECOPD,

NCT01422681), in which the efficacy of the Decap Smart in reducing the intubation rate or the duration of invasive mechanical ventilation in patients with COPD, treated either with NIV or invasive mechanical ventilation (IMV), will be addressed. Thus, pending results will hopefully expand and confirm the efficacy of minimally invasive extracorporeal CO₂ removal strategy in COPD exacerbation.

26.6 Thoracic Surgery

More recently, extracorporeal CO₂ removal support has been successfully applied to patients who underwent elective or emergent thoracic surgery. In this scenario, extracorporeal CO₂ removal support makes one lung ventilation feasible in patients with severe impairment of alveolar ventilation in whom prolonged apneic ventilation is also required.

In an observational study, Wiebe et al. showed that the pumpless extracorporeal CO₂ removal device—Novalung—was a safe and feasible tool in patients with poor respiratory function who underwent major thoracic surgery. In fact, ten patient candidates for elective or emergent thoracic surgery were supported by pumpless artero-venous bypass. Indications for the intraoperative application of the Novalung were hypoxic respiratory failure (defined by PaO₂/FiO₂ < 150) that impeded one lung ventilation (6 patients) and prolonged periods of apnea required during surgery (four patients). The Novalung produced only small oxygen transfer (49.2 ± 4.4 ml/min) and remarkable clearance of CO₂ (121 ± 18 ml/min). In fact, paCO₂ decreased significantly from 58.4 ± 27 to 37 ± 9 mmHg and pH increased from 7.24 ± 0.2 to 7.45 ± 0.04 . Blood flow across the Novalung A-V was 1.58 ± 0.3 l/min (1.2–2.2 l/min) and the blood pressure was maintained with a low dose of norepinephrine [16]. The only device-related complications observed were a retroperitoneal hematoma after percutaneous removal of an arterial cannula and a delayed extubation due to hypothermia.

These results were expanded in a small series of patients with ARDS following the repair of the bronchopleural fistula. In fact, Hommel and colleagues showed that ultra-protective mechanical ventilation, consisting of low inspiratory pressure plus extracorporeal assistance, minimized the risk of barotrauma and VILI. Moreover, at 4 days of treatment, there was a significant reduction of tidal volume (from 5.1 ml pre-bypass to 2.8 ml PBW) and plateau pressure (from 32.4 to 27.6 cmH₂O), while PaCO₂ decreased from 73.6 to 54 mmHg and pH was normalized [15].

26.7 Bridge to Lung Transplantation

Extracorporeal carbon dioxide removal systems have been recently used in patients with advanced lung diseases waiting for lung transplantation. In fact, lung transplant waiting lists hold a high mortality rate, which is the highest compared to other solid organ transplants. The progression of the underlying disease, or the occurrence of supra-imposed lung infections, often requires the use of invasive

mechanical ventilation as a support measure [27]. Evidence exists that mechanical ventilation before lung transplantation can further enhance the initial lung damage and lead to multiorgan dysfunction, resulting in clinical unsuitability for lung transplantation (“too sick to be transplanted”) [28]. In addition, MV is a significant risk factor for mortality after lung transplantation and certainly needs to be avoided.

In several reports at single centers, extracorporeal supports ranging from minimally invasive CO₂ removal system to full ECMO have been used to support patients with advanced respiratory failure unresponsive to maximal MV support, as defined by high concentration of inspired oxygen, severe hypercapnia, use of nitric oxide, and high levels of PEEP [17]. Of interest, midterm patient outcomes and allograft function of patients treated with ECMO were similar to those who did not receive this support before lung transplant [29, 30].

Recently, in a non-matched case control study, Fuehner and colleagues showed that ECMO is a valuable supportive therapy as a bridge to lung transplantation for non-intubated patients with end-stage lung disease. Compared to 34 historical control patients supported with invasive mechanical ventilation, 26 awake patients treated with ECMO had better outcome in terms of graft survival. In fact, survival at 6 months after lung transplantation was significantly higher in the ECMO group (80 % vs. 50 %, $p=0.02$). Moreover, duration of support (9 vs. 15 days) and percentage of patients that were transplanted (23 % vs. 29 %) were similar in both groups [18]. These data suggest that supporting patients with extracorporeal support instead of invasive mechanical ventilation may improve patients’ homeostasis and, consequently, graft function.

26.8 Complications of ECMO and ECCO₂R Support

Since 1976, a constant decrease in ARDS mortality in patients treated with extracorporeal devices was reported [31, 32]. In recent years, crucial progresses have been made in the conception and construction of ECMO circuits, heparin-bonded cannulae, rotary pumps, and small efficient long-lasting oxygenators. They are now simpler and safer and require less anticoagulants, thus being associated with fewer bleeding complications. These improvements in ECMO technology, along with an intensive training of the ICU staff, lead to safer and more effective ECMO application.

The ECMO experience matured during the past H1N1 pandemic spread, producing a wide array of data on ECMO complications. Hemorrhagic complications occurred in half of the patients during ECMO therapy, with the most common sources being ECMO cannulation sites in up to one-fifth of all patients. Less bleeding, observed in a tenth of the patients, was found in the gastrointestinal tract, respiratory tract, vaginal site, and brain [33]. Moreover, in a retrospective study of the ELSO registry from 1986 to 2006, complications of ECMO were analyzed: over time, circuit rupture and pneumothorax became less frequent, but circuit clots, renal insufficiency, renal replacement therapies, pulmonary hemorrhage, inotropic medications, hyperglycemia, extremes of pH, arrhythmias, and hypertension became

more common [34]. Another widespread complication during ECMO is represented by infection. A retrospective study of post-surgery ECMO showed that infection complications occurred in 42 patients (62 %), with the most common sites being the respiratory tract in 30 patients (44 %) and bloodstream in 14 patients (21 %). Moreover, non-ECMO catheter-related infections occurred in 13 patients (19 %) and ECMO cannula-related infections in 7 patients (10 %) [35]. Another cannula-related adverse event was reported during the positioning of a bicaval dual-lumen cannula for VV ECMO via the internal jugular vein: the cannula migration into the right ventricle, resulting in right ventricular rupture and cardiac tamponade [36].

PECLA device can remove up to 50 % of the total body CO₂ production, with a blood flow of around 1 l/min, and can transfer 20–60 ml/min of oxygen. Moreover, these devices can also be utilized in patients with high risk of bleeding because the cannula and device are heparin coated and also because they require the same dose of anticoagulation therapy used in immobilized critically ill patients [37].

In a retrospective experience published by Bein et al. in 2006, it was reported that the incidence of serious malfunctioning was at 24.4 %. The complications associated were bleeding during cannulation and formation of hematoma at the insertion site. An episode of ischemia and compartmental syndrome of a lower limb were also reported [33]. As recently reported by Sanchez et al. during the PECLA period, several plasma markers increased significantly. Even though these changes were statistically significant, none of the parameters reached pathologic levels within or after the PECLA period. Moreover, alterations showed no clinical relevance and normalized within 48 h after its removal [10].

Many fewer complications have been described with new veno-venous ECCO₂R systems because of their less invasiveness. In a prospective study on patients with ARDS, in which the ECCO₂R system Decap was used to allow protective mechanical ventilation with tidal volume less than 6 ml/kg, no patient-related complications were observed. In three cases, the 14-French double-lumen catheter had to be replaced by two 8-French simple-lumen catheters (one for each femoral vein) due to recirculation issues (two cases) and catheter kinking (one case). The membrane clotting, which has been observed in three patients, did not result in additional transfusion [12]. Moreover, in a cohort of 20 COPD patients treated with the ECCO₂R system—Hemolung—single death due to internal hemorrhage from vessel perforation was described, although it is not directly attributable to this device. In addition, heparin-induced thrombocytopenia was described as a more common side effect, although this was not associated with clinically significant bleeding [14].

26.9 Conclusions

The continuous technological improvement of ECMO and ECCO₂R systems caused a widespread use of this technique despite the lack of solid clinical data assessing safety, efficacy, and cost-effectiveness. Based on the goal of treatment to achieve, modulation of treatment invasiveness seems to be prudent; in fact, as early in the

story of extracorporeal support, this powerful life-sustaining therapy may be obscured whether risks as serious hemorrhagic complications will stand above benefits. Clinical trials assessing the balance between risk and benefit of this powerful therapy are needed.

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27.1 Introduction

Discontinuing extracorporeal respiratory support is a crucial step in patient management, but deciding when and how to wean patients represents a significant challenge for ICU physicians. Due to the lack of definite criteria, the decision is usually based on the personal experience and clinical judgment of attending physicians; however, some indications come from guidelines of scientific societies, local hospital protocols, or published case series.

In the following paragraphs, we will discuss the following aspects of the weaning process: (a) When is a patient ready for weaning? (b) How is weaning performed? (c) How is ventilation managed during the weaning process?

27.2 Assessment of Patient Readiness for Weaning

As described above, the extracorporeal support is progressively reduced as the native lung function improves. To establish if a patient is ready for weaning off ECMO, we recommend a thorough assessment of his respiratory function, based on the variations of the following functional parameters during the course of the disease:

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- (a) Increase of the fraction of oxygen delivery provided by the native lung compared to that provided by the artificial lung. According to the ELSO Guidelines [1], ECMO discontinuation can be considered when the native lung is supporting 50–80 % of total gas exchange. In a large cohort of ARDS patients treated with ECMO, Mols et al. reported weaning off ECMO when at least 80 % of total oxygen delivery was supplied by the patient's own lung [2].
 - (b) Improvement of respiratory mechanics, e.g., increase of static compliance of the respiratory system (in ARDS patients) and/or reduction of airway resistance (in patients with severe asthma).
 - (c) Improvement of gas exchange: most authors indicate that the patient can be considered for weaning when arterial pO_2 and pCO_2 are adequate at “moderate ventilator settings” (i.e., $FiO_2 \leq 0.6–0.5$ and relatively low PEEP), but do not provide clear-cut threshold levels of these parameters.

27.3 Discontinuation Procedure

The extracorporeal support is reduced in parallel with the improvement of native lung function.

Severely hypoxemic patients require high extracorporeal blood flow: once the native lung starts to heal and to contribute significantly to arterial oxygenation, the extracorporeal blood flow can be progressively reduced (Fig. 27.1).

On the other hand, in purely hypercapnic patients, the extracorporeal blood flow is low from the beginning and the magnitude of the assist will depend on the sweep gas flow.

In the first phases, the FiO_2 of the sweep gas is usually kept at 100 %, especially in hypoxemic patients. As gas exchanges improve, it is suggested to reduce the FiO_2 of the ventilator before that of the sweep gas, to avoid oxygen-related toxicity on the native lung.

During the weaning phase, different strategies of mechanical ventilation can be adopted.

In some patients, for example those with serious bleeding complications, the priority is to discontinue ECMO as soon as possible; in these cases, patients will be disconnected from ECMO while still on controlled mechanical ventilation.

More commonly, ECMO is used to facilitate the switch from controlled mechanical ventilation to an assisted spontaneous breathing mode, such as Pressure-Support Ventilation (PSV) or Neurally Adjusted Ventilatory Assist (NAVA) [3, 4]. In this case, there is a complex interplay between sedation, respiratory drive, and ventilation of the artificial lung; for example, increasing the sweep gas is a very efficient mode to control the respiratory drive of the patient and may allow a reduction of sedative drug dosage. In other words, modulating the extracorporeal assist becomes a strategy to facilitate the patient's weaning from the ventilator.

Finally, there are situations where it is desirable to reduce as much as possible the duration of invasive mechanical ventilation, such as in presence of severe immunocompromise: in these cases, patients can be extubated while still on ECMO, and the extracorporeal support is discontinued only after separation from the ventilator.

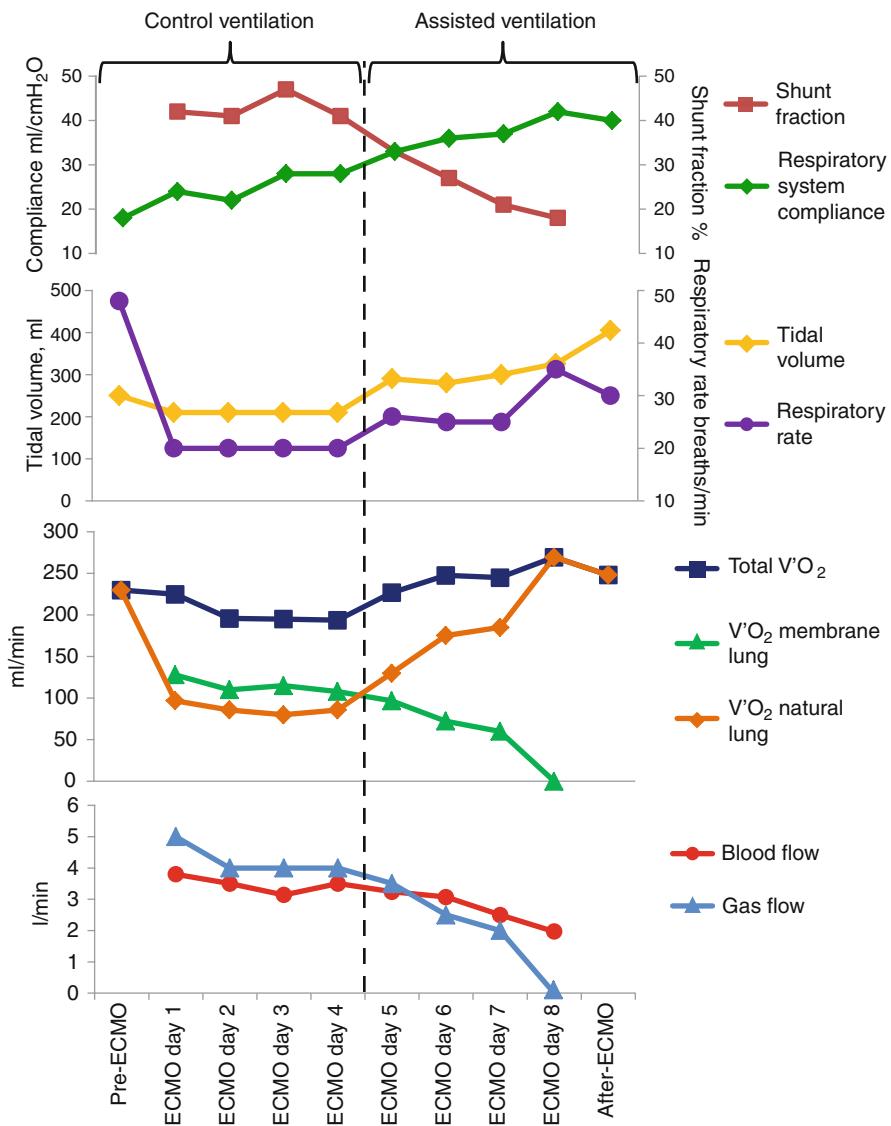


Fig. 27.1 Example of daily ventilatory management in an ARDS patient. Main parameters of ventilator and ECMO setting, gas exchange, and hemodynamics are shown day by day. As soon as the native lung improves, the patient is switched to assisted mechanical ventilation (dotted line), and mechanical and ECMO GF support is progressively reduced

27.4 Trial of ECMO Discontinuation

Once the patient is judged as ready for weaning according to the criteria listed above, it is recommended to perform a trial of temporary discontinuation of the extracorporeal support. By definition, venovenous ECMO does not provide hemodynamic support: for this reason, unlike with venoarterial ECMO, there is no need for stopping or reducing extracorporeal blood flow at the time of the trial off.

The trial of venovenous ECMO discontinuation should be performed as follows:

- If the patient is on controlled mechanical ventilation, the ventilator settings (respiratory rate, plateau pressure, FiO_2 , and PEEP) should be adjusted to values that are considered acceptable off ECMO. If the patient is on assisted spontaneous ventilation (e.g., PSV, ACV, NAVA), an adjustment of the level of inspiratory assist and a careful modulation of the level of sedation may be required.
- Once the ventilator settings have been adjusted as described before, the sweep gas to the oxygenator is turned off. It should be remembered that it is not enough to turn the flowmeter to zero, but it is necessary to clamp the gas tubes, since oxygen can leak around the flowmeter even when it appears to be off. Once the sweep gas flow is stopped, the oxygen will be fully consumed after about 20 min: monitoring of venous oxygen saturation on the extracorporeal circuit will indicate when the excess oxygen in the circuit has been used up.
- The extracorporeal blood flow is continued, and no adjustment of heparin dose is required.

There are no clear indications on the duration of the trial: some centers suggest a trial off for 1–6 h, but if needed the duration of the trial can be prolonged up to several hours. During this period, the patient should be closely monitored, paying particular attention to the following aspects:

- Hemodynamic stability: besides standard hemodynamic parameters (heart rate, arterial blood pressure, cardiac filling pressures), continuous monitoring of mixed venous oxygen saturation (if available) is recommended to evaluate the adequacy of oxygen delivery during ECMO discontinuation.
- Adequacy of gas exchanges (serial monitoring of arterial blood gas analysis).
- If the patient is on an assisted spontaneous mode of ventilation, respiratory pattern (tidal volume, respiratory rate, minute ventilation) and mechanics (signs of distress, use of accessory muscles) should be carefully assessed.

If the patient remains stable during the trial and, most importantly, his ventilatory load is acceptable, the extracorporeal support can be definitively discontinued and the cannulas removed as described below (Fig. 27.2).

In particularly unstable patients, some centers tend to disconnect the circuit leaving the cannulas in place to allow a prompt reinstitution of the extracorporeal support in case of sudden deterioration of the patient's conditions (Fig. 27.3). Venous cannulas can be left in place for up to 48 h: to avoid clotting, they should be flushed with a drip of heparinized solution and systemic anticoagulation continued at unchanged dosage.

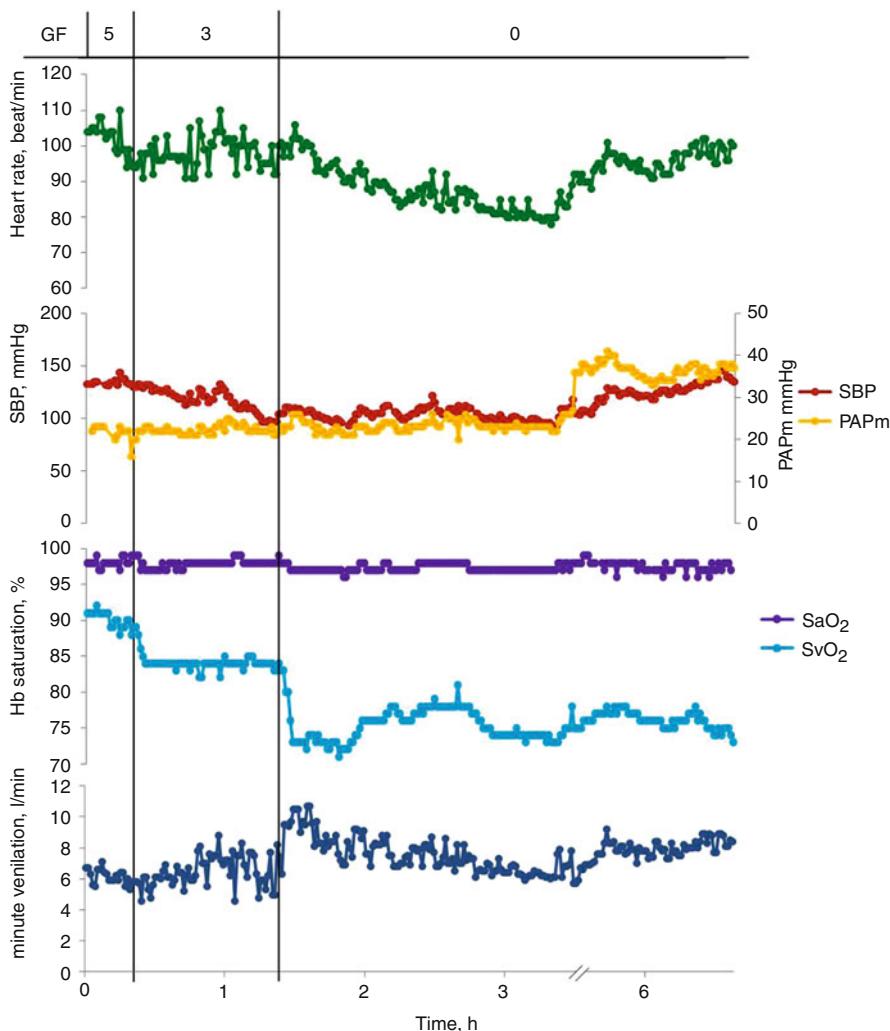


Fig. 27.2 Example of a successful trial of ECMO discontinuation. ECMO gas flow (GF) is decreased from 5 to 3 to 0 l/min. In spite of the fall in mixed venous oxygen saturation (SvO_2), arterial oxygen saturation (SaO_2) remains stable with a reasonable increase in minute ventilation and hemodynamic drive. The patient was successfully decannulated

27.5 Decannulation

Cannulas placed percutaneously can be removed directly. Some centers propose to turn off heparin for 30–60 min before decannulation. Before cannula removal, a purse-string suture is inserted around the cannulation site. Immediately after decannulation, the suture is tightened and local pressure is applied for at least

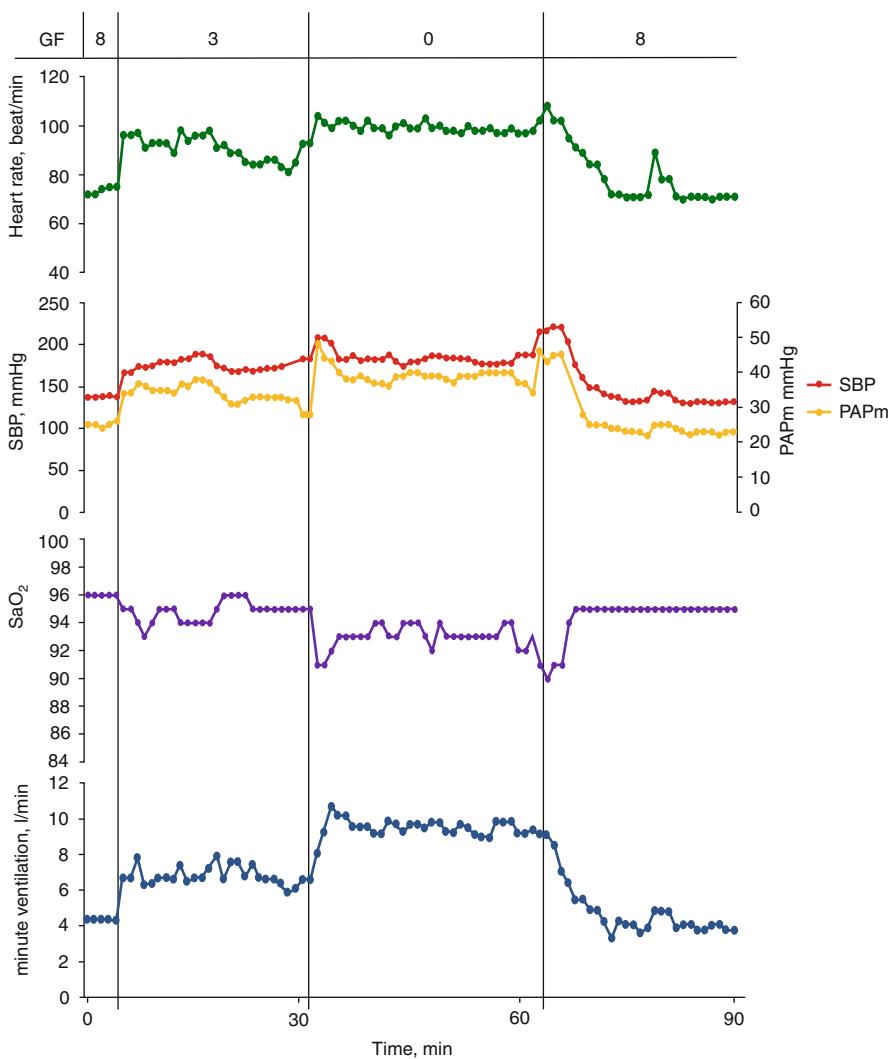


Fig. 27.3 Example of a failed trial of ECMO discontinuation. ECMO gas flow (*GF*) is decreased from 3 to 0 l/min. As soon as *GF* is turned off, minute ventilation doubles and arterial oxygen saturation decreases while the heart rate and systemic blood pressure increase. The increase in minute ventilation and the decrease in SaO_2 were considered unacceptable. *GF* was returned to 8 l/min to allow patient rest

30 min. It is advised to check regularly the cannulation site for signs of bleeding or hematoma formation.

When removing venous cannulas (especially jugular catheters) in spontaneously breathing patients, there is a potential risk of air aspiration through the catheter's side holes: to avoid this, a Valsalva maneuver on the ventilator should be performed at the time of cannula removal.

After decannulation, we perform a venous Doppler of the lower limbs and of the cannulated vessels to exclude thrombotic events.

27.6 Discontinuation for Futility

The extracorporeal support should be discontinued for futility if the patient's conditions evolve toward a permanent and irreversible damage of brain, lung, and/or heart function, and there is no hope of recovery or organ replacement. According to the ELSO Guidelines [1], this possibility should be explained to the family before ECMO institution.

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Part IV

ECMO for Organ Procurement

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28.1 Introduction

Transplantation is currently considered to be an effective therapy for treating end-stage organ diseases. However, the widespread application of organ transplantation is limited by the shortage of viable donor organs. This shortage has been addressed by various measures: improvements in brain death donor (BDD) management by means of aggressive support, extension of the acceptance criteria for marginal donors, and the implementation of protocols that accept donation after cardiac death (DCD). This latter measure has created a donor group that is frequently referred to as non-heart-beating donors (NHBDs) [1]. In countries where legal or societal barriers discourage the use of brain death donors, DCD donors are the only alternative source of organs for transplantation when no living donors are available [2]. NHBDs are classified, in accordance with the Maastricht criteria [3], into the following four categories: donors who are declared dead outside the hospital and are brought into the hospital without any attempt at resuscitation (Type 1), donors in whom cardiac arrest occurs unexpectedly and for whom resuscitation attempts are unsuccessful (Type 2), donors for whom cardiac arrest is expected after withdrawal of treatment (Type 3), and donors in whom cardiac arrest occurs during or after brain death diagnostic procedures (Type 4). Types 1 and 2 are defined as uncontrolled donors on

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Table 28.1 Maastricht NHBD categories

Category	Description	Alternative categorization
I	Dead on arrival	Uncontrolled
II	Unsuccessful resuscitation	Uncontrolled
III	Awaiting cardiac arrest	Controlled
IV	Cardiac arrest while brain death	Controlled

the bases of unexpected cardiac arrest and unsuccessful resuscitation. In contrast, Types 3 and 4 are defined as controlled donors. Type 3 donors occur after a decision that care is “futile” and the consequent removal of life-sustaining treatment, such as mechanical ventilation or organ perfusion support (Table 28.1).

The main impediment to NHBD is the increased incidence of complications or of impaired graft function as a result of extended periods of warm ischemia. A univocal definition of warm ischemia time (WIT) has yet to be agreed. In controlled DCD, WIT can be defined as the interval between support withdrawal and cold perfusion onset [4] or as that between the withdrawal of life support and cardiac arrest; this interval is also known as the “agonal phase” [5]. It is characterized by sustained hypotension and may impact substantially on warm ischemic damage to DCD organs. Research has shown that agonal periods of more than 2 h duration are not acceptable for transplantation purposes [6]. In uncontrolled DCD, WIT can impact even more significantly, since the exact period of circulatory arrest is usually not known [7]. Furthermore, between cardiac arrest and cold perfusion start, there is a period of cardiopulmonary resuscitation (CPR) of variable duration and efficacy. It has recently been shown that the use of automated chest compression devices may improve organ perfusion before the organ preservation measures are initiated [8]. An apparently clear finding is that static hypothermic storage may not be the most appropriate strategy for DCD graft preservation, because hypoxia and reperfusion can exacerbate ischemic tissue damage. Research and clinical practice have accordingly pursued the development of several strategies to prevent warm ischemic injury and improve organ preservation in DCD donors.

28.2 Preservation Strategies for DCD Donors

There are two current perfusion techniques:

- *“In situ” perfusion cooling*: Introduced in the early 1970s and subsequently modified, this technique effects cold perfusion (4 °C) by means of a double-balloon triple-lumen (DBTL) catheter that is inserted through the femoral artery into the aorta; the thoracic and abdominal balloons are then, respectively, inflated immediately above the renal arteries and the aortic carrefour. An infusion system is then connected to the catheter to enable flushing with a total of 15–20 l of cold preservation solution, such that the kidneys cool to 10–15 °C. Blood drainage is enabled by a large Foley catheter that is introduced into the femoral vein [9]. Donor nephrectomy can be performed within 2 h of flush perfusion. This is an easy technique with which to preserve kidneys both in controlled DCD and in specific

cases of uncontrolled DCD. However, this procedure is affected by technical complications, and grafts harvested from these donors show an increased incidence of delayed graft function (DGF) and acute tubular necrosis (ATN) [10].

- **Extracorporeal membrane oxygenation (ECMO):** ECMO is widely applied as systemic supply for circulatory and respiratory support. In DCD, it can be used to restore warm and oxygenated blood flow through the organs and thus to provide adequate tissue perfusion between death and organ procurement. Two different perfusion methods have been described:
 - *Total body cooling (TBC) or “core cooling”* at 18 °C through cardiopulmonary bypass (CPB). Originally used in BDD for heart and lung procurement [11], this method was applied in the early 1990s to NHBD and provided acceptable results for kidney and liver transplantation. However, an increased incidence of DGF has been observed in kidney transplantation [12, 13].
 - “*Selective*” *ECMO*, exclusively for abdominal organs perfusion. There are two variants of the technique:
 - *Hypothermic ECMO:* The technical problems encountered using TBC to obtain profound hypothermia have prompted many centers to develop a selective hypothermic form of ECMO [11]. In combination with a temperature-controlled heater-cooler, the ECMO system is placed into the femoral venoarterial route. An occlusion balloon catheter is inserted through the contralateral artery to occlude the thoracic aorta, and femoral arteries are ligated bilaterally. With this system, progressive cooling enables the maintenance of a steady 4 °C temperature in abdominal organs perfused with oxygenated blood. Unfortunately, hypothermic ECMO has a limited capacity to improve cellular function because metabolic activity is almost completely shut down at such reduced temperature [14]. For this reason all the cellular repair processes are impaired by this organ preservation strategy.
 - *Normothermic ECMO (NECMO):* This more recent technique consists in normothermic perfusion of the abdominal organs at 37 °C with oxygenated blood [15]. The current evidence suggests the NECMO reliably serves to reverse ischemic lesions, improve tissue microcirculation, and ultimately improve the viability of suboptimal graft [16].

28.3 The NECMO Technique

The femoral artery and vein are, respectively, cannulated (surgically or percutaneously) with 15–19 Fr and 21–24 Fr perfusion catheters. The cannulae are connected to the tubing of an ECMO circuit. The ECMO circuit consists in a reservoir, a centrifugal pump, and a blood oxygenator connected to a heat exchanger and a gas (O₂/air) source (Fig. 28.1). The circuit is primed with saline solution. The contralateral femoral artery is cannulated with a Fogarty balloon catheter, which is advanced into the supraceliac aorta. The balloon is inflated to prevent cardiac and brain perfusion. Proper positioning of the balloon is confirmed by chest radiography. Pump flow is maintained at between 1.7 and 3 l/min, temperature at 35.5–37.5 °C, and pH at

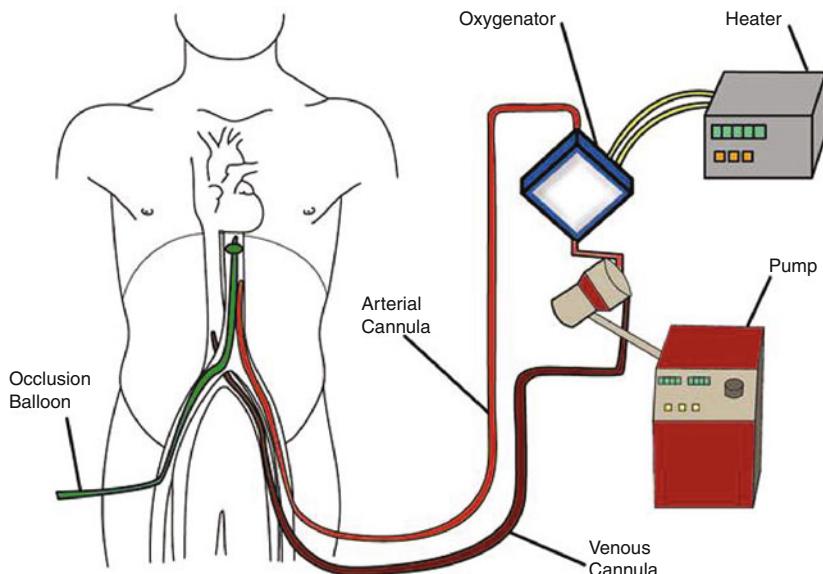


Fig. 28.1 Normothermic extracorporeal membrane oxygenation (NECMO)

7.0–7.4 [17, 18]. Post-oxygenator arterial blood gas is sampled at baseline and throughout NECMO to determine oxygenation parameters and acid-base status. The circuit sweep gas levels (FiO_2 and flow rate) are adjusted to keep PaCO_2 at between 30 and 45 mmHg and SaO_2 at about 98–100 %. Sodium bicarbonate should be added to the circuit to correct metabolic acidosis. Anticoagulation is started with full heparinization (3 mg/kg) prior to cannulation and is subsequently maintained by heparin bolus of 1.5 mg/kg, in accordance with ACT values.

NECMO is continued until cold perfusion is performed at organ retrieval. The abdomen is thoroughly explored, and retrograde *in situ* flush is performed with ice cold preservation solution via the arterial cannula, to perfuse the liver and the kidneys. It is only necessary to perform one additional venous cannulation in order to perfuse the portal vein. At this point, NECMO is discontinued, the arterial line is clamped distally to the oxygenator and proximally to the preservation solution perfusion line, and venous return is collected by means of field suction [17, 19].

28.4 The Physiology of NECMO

Experimental normothermic ECMO studies started around 1997 in Spain and in Japan [11, 19]. They described this technique as playing a protective role in organ function preservation by maintaining tissue perfusion under controlled conditions. The protection consists in the ability of normothermic organs to recover *in situ* from warm ischemic damage and in the provision of oxygen and nutrients at

physiological temperature to restore metabolic processes, which in turn enable the repair of damaged cells, the correction of acidosis prior to cold ischemia, the restoration of depleted ATP, the regulation of calcium homeostasis, and the removal of free radicals. The avoidance of cold ischemia by continuous normothermic perfusion is the other obvious advantage of NECMO [20]. It enables improvement in the quality of abdominal graft (kidneys and livers) and the reversal of ischemic damage. Blood has been shown to be better than crystalloids for the maintenance of membrane integrity and hence for recovery from tissue damage. On the other hand, since lower temperatures rapidly reduce metabolism, normothermia is the most favorable condition for the restoration of metabolic processes, for the repair of damaged cells, and for the reinvigoration of metabolite energy levels. According to Net et al. [16], NECMO could shift warm ischemia time toward an ischemic preconditioning period and thus provide DCD donors with greater viability. This technique was first applied to clinical practice in the early 2000s in the USA, Spain, and Japan.

28.5 Normothermic ECMO in Uncontrolled NHBD

Normothermic ECMO is the preferred approach for uncontrolled NHBDs in Spain, in France, and, more recently, in Italy too [21–23]. Patients with witnessed out-of-hospital refractory cardiac arrest (CA) are considered eligible. The emergency medical service is mobilized to the scene of witnessed CA, where it starts advanced life support in accordance with the international standard guidelines and using an automated chest compression system [24]. If the asystolic period persists for at least 20–30 min and no reversible cause is identified, the CA may be considered to be irreversible and further attempts at resuscitation futile [25]. If an out-of-hospital patient fulfills Type 2 donor criteria, he is maintained on an automated chest compression system and transferred to hospital. The declaration of death is made in the hospital, on the basis of the absence of ECG and spontaneous respiratory activity for at least 5 min. Subsequently, heparin is administered and external cardiac massage is restarted with automated chest compression. At the same time, femoral cannulations are performed, NECMO is started, and mechanical ventilation and the chest compressor are removed. A Fogarty balloon catheter is inserted through the contralateral femoral artery and inflated in the supraceliac aorta. NECMO continues to be applied if prior consent for donation is in hand. During this period, the donor is evaluated for possible contraindications to donation. The criteria for donation include the following: witnessed arrest; no-flow period without CPR limited to a maximum 15–20 min; age below 60 years for kidneys, 50–55 for lungs and liver; cause of death known or presumed; and non-bleeding abdominal injuries [21, 22]. The time limits for the interval between cardiac arrest and organ perfusion, and between cardiac arrest and organ retrieval, have, respectively, been set at 120 and 240 min. These limits offer two major benefits: They give the next of kin more time (as much as 4 h) to accept the death and to consider donation and they prolong organ perfusion under controlled physiological conditions.

Accordingly, liver and kidney tests can be performed, and their functions can be biochemically evaluated [26]. It has been reported that DCD Type 2 kidneys undergoing NECMO showed a lower rate of DGF and primary graft nonfunction (PGNF) than did kidneys used after hypothermic preservation [27]. Although the DGF levels reported for NHBD are consistently high (16–20 %) even under NECMO, this effect appears to be transient and not to impact on the posttransplant outcome. In kidneys from UNHBD undergoing NECMO, the 1-year graft survival rate has been reported to be as high as 87.4 % [24]. The use of liver from these donors is somewhat problematic because immediate organ function is mandatory for the recipient's survival. Major concerns in this respect initially emerged from initial series to use uncontrolled DCD liver grafts; specifically, an increased incidence of ischemic cholangiopathy and of subsequent primary graft nonfunction was observed [25]. Despite the encouraging results they obtained in liver transplantation from uncontrolled DCD, Fondevila et al. reported respective 1-year recipient and graft survival rates of 82 and 70 %, even though only 10 % of grafts from Type 2 DCD donors had been used [28]. More recently, in Madrid, a lung transplantation program that uses uncontrolled DCD donors was launched [29]; the said program developed a new multiorgan preservation methodology that is also called “bithermia preservation.” In this methodology, abdominal organs are preserved in NECMO, and the thoracic organs are kept in hypothermia by means of continuous pneumoplegia perfusion [29, 30].

28.6 Normothermic ECMO in Controlled NHBD

In the USA and Northern Europe, NECMO is applied in those patients for whom a “futility” of care decision has been made, usually by intensive care staff and other treating physicians [31, 32]. When the planned withdrawal of life-sustaining support is discussed with the relatives of patients who have a nonreversible neurological injury, organ donation can be an appropriate consideration. Having used NECMO for abdominal organ perfusion in controlled DCD donors, Migliocca et al. reported very low DGF levels (8 %) and proposed that this procedure could expand the kidney donor pool by one third.

Before withdrawal of treatment and after the family's consent, the cannulae for NECMO are placed at the bedside in ICU. Life support is withdrawn and comfort measures are continued. If death occurs, it is declared after a “no touch” period (generally around 5 min) and NECMO is started. A balloon catheter is placed in the thoracic aorta, to prevent the oxygenated blood returning to the heart, thus avoiding functional recovery. In some centers, if cardiac death does not occur within 60 min, the patient is no longer considered a candidate for DCD donation [17, 33]. Survival rates for kidney transplant from ECMO-controlled DCD are comparable with those for kidneys from brain-dead donors [34]. Despite favorable outcomes reported by certain centers, graft survival is consistently lower in liver than in kidney

transplantation. More rigorous selection is mandatory for liver transplantation as a more precise definition of donor-specific risk factors. Increasing experience in DCD liver transplantation has enabled the definition of the donor-specific risk factors that are associated with poor graft survival, namely, donor WIT >20–30 min, cold ischemia time >8–10 h, and donor age >40–60 years [35]. However, single centers have reported favorable DCD outcomes and equivalence in DCD-BDD outcomes for liver transplantation [32].

28.7 ECMO Assistance for Brain-Dead Donors (BDD)

In some countries, ECMO has been used to support BD multiorgan donors in whom it is not possible to complete death assessment for cardiac or respiratory failure [13, 36]. ECMO support is an option in hemodynamically unstable donors, who require three different inotropes and vasopressors or with an inotrope score >30 to maintain mean arterial pressure >60 mmHg. Other candidates for ECMO support are donors with a $\text{PaO}_2/\text{FiO}_2$ ratio <200 mmHg (at FiO_2 100 % and high level of PEEP) and in whom hypoxemia precludes the apnea test [37, 38]. In these cases, systemic ECMO begins during brain-death assessment. Despite this being an uncommon use for ECMO, single centers have demonstrated that early ECMO support for unstable BDD is a feasible strategy to increase the donor pool and to preserve donor organs. It reduces vasoactive drug doses, which in turn may lower the incidence of primary graft dysfunction, especially after heart transplantation. Under ECMO, apnea test should be performed with the gas flow to the oxygenator lowered to zero, so that oxygen supply and ventilation are completely dependent on the ventilator [36]. In selected BD donors, prompt ECMO could thus play a role in recovering viable organs which otherwise would have been lost.

28.8 The Future

Organ procurement strategies for the future will center on exact evaluation of the viability of DCD-sourced organs for transplantation purposes. To this end, the underlying procedures will necessarily include the option of an adjunctive period of normothermic “ex vivo” recirculation [38]. In theory, the use either of normothermic machine perfusion (NMP) after kidney and liver procurement or of ex vivo lung perfusion (EVLP) after lung procurement will allow physiological aerobic metabolism to continue, which in turn will provide affected organs with specific substrates and thus enable the reversal of warm ischemic injury [39, 40]. Analogously, time will have to be invested in, and in the long term saved by, exact evaluation of the quality of the organs themselves. Periods of 3–6 h of ex vivo perfusion, depending on which organs are involved, seem to be necessary to reverse ischemic damage and to enable pre-transplant assessment of organs. Furthermore, normothermic in vivo and ex vivo recirculation offer an invaluable platform upon which to introduce potential therapies that target ischemia/reperfusion injury and acute rejection after transplantation.

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29.1 Introduction

Transplantation is considered a valuable option in the treatment of end-stage lung disease. However, organs from multiorgan donors available for transplantation are far less than the number of potential recipients, so that as many as 15–20 % of them die while on a waitlist [18].

Over the years, a number of ways to overcome the discrepancy between the need and the availability of organs have been explored, including the use of lung allocation scores and the implementation of standardized donor management protocol [7]. In the last decade, several authors have extended lung donor criteria to increase the pool of organs, unfortunately with controversial results.

Recently, the feasibility and safety of transplanting high-risk donor lungs that have undergone ex vivo lung perfusion (EVLP) have been successfully documented [15, 16]. The technique has brought into a new era of lung transplantation. In fact, EVLP not only has allowed for expansion of the pool of lungs available for transplantation, but it has also deeply challenged the concept of lung suitability itself. In fact, organs previously not considered for transplantation are now safely used with outcomes similar to those of standard donor lungs [1, 4, 5, 8, 20–22].

The concept of extracorporeal evaluation and treatment of lung function before transplantation date back to 1970 [9]. However, a renewed interest on

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Table 29.1 Published clinical experiences on EVLP

		EVLP donors			EVLP → Lung transplant
		Year	DBD	DCD	
Ingemansson	Ann Thor Surg	2009		×	Yes
Pego-Fernandez	Rev Bras Cir Cardiovasc	2010	×		No
Cypel	New Engl J Med	2011	×	×	Yes
Madeiros	J Heart Lung Transpl	2011	×		No
Sedaria	Ann Thor Surg	2011	×		No
Cypel	J Thorac Cardiovasc Surg	2012	×	×	Yes
Aigner	Am J Transplantation	2012	×		Yes
Valenza	Transp Proc	2012	×		Yes
Zych	J Heart Lung Transpl	2012	×	×	Yes
Wallinder	J Thorac Cardiovasc Surg	2012	×		Yes
Wallinder	Eur J Card-Thor Surg	2013	×		Yes

extracorporeal lung perfusion has started with the clinical experience of Ingemannsson and colleagues who showed initially rejected donor lungs were reconditioned to acceptable function, and in six recipients, double lung transplantation was performed with a 3-month survival of 100 % [8]. The pivotal role of EVLP has been further fostered by the study of Cypel et al. that showed no inferiority of clinical transplantation of lungs retrieved from high-risk donors and reconditioned by EVLP [4]. A number of lung transplantation centers have since then taken the challenge of implementing clinical EVLP programs (Table 29.1).

29.2 Technique

Figure 29.1 shows the circuit used to perfuse the isolated lungs. It consists of a blood reservoir (1 in the figure) connected to a gas oxygenator with a built-in heat exchanger (2), a centrifugal pump (3), a leukocyte arterial filter (4), and a non-heparin-coated polyvinyl tubing. The system is primed with Steen solution™ (Vitrolife, Gothenburg, Sweden). This is a specifically designed buffered solution with an extracellular-type composition and with an optimized albumin-based colloid osmotic pressure. Methylprednisolone, antibiotics, and heparin are also added to the perfusate. To run the EVLP, the lungs procured from donors and cold stored on ice are contained in a specifically designed chamber (XVIVO, Vitrolife). Temperature of the perfusate is gradually increased to a target temperature of 37 °C over approximately 30 min. Once the lung outflow temperature exceeds 32 °C, mechanical ventilation of the lungs is started. The circuit oxygenator is used unconventionally during EVLP; in fact, gas flow through the artificial lung is composed of CO₂ and air and is intended to add CO₂ and remove O₂ so that the perfusate composition is similar to that of the pulmonary artery. The lungs are ventilated and perfused up to 4 h in most protocols, at the end of which, a final evaluation of lung function is performed. This takes into account parameters of lung perfusion (perfusate flow, temperature, and pulmonary artery pressure, pulmonary vascular resistance) and ventilation (tidal volume, airway pressure, dynamic compliance,

Fig. 29.1 Figure shows the circuit used to perfuse the isolated lungs. It consists of a blood reservoir (1) connected to a gas oxygenator with a built-in heat exchanger (2), a centrifugal pump (3), a leukocyte arterial filter (4), and a non-heparin-coated polyvinyl tubing

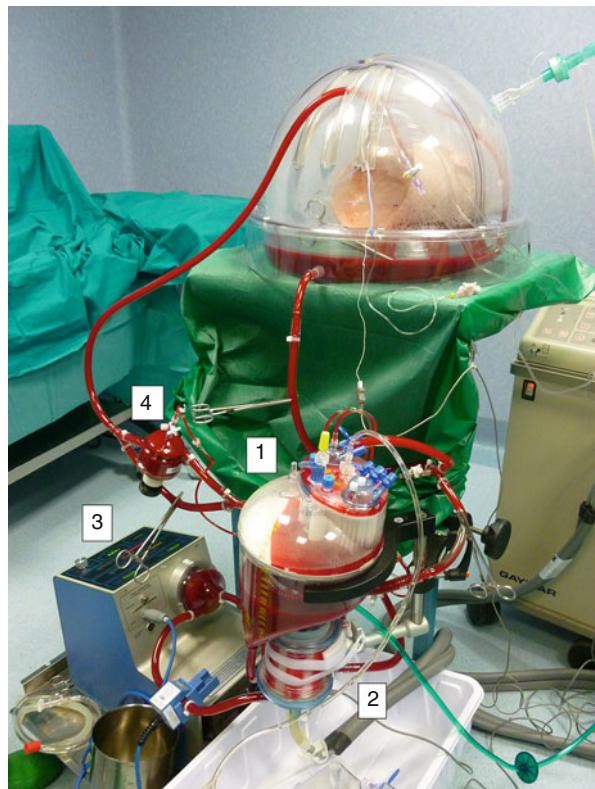


Table 29.2 Comparison between the Lund and Toronto EVLP protocols

	Lund	Toronto
Duration, hours	1.5	4
Perfusate flow, % donor CO	100	40
Pulmonary artery pressure, mmHg	<20	10–15
Left atrium	Open	Closed
FiO ₂ , %	50	21
Tidal volume, mL/kg donor's weight	5–7	7
Respiratory rate, bpm	15–20	7
Perfusate composition	Cellular	Acellular

respiratory rate, PEEP and FiO₂), together with analysis of partial pressures of oxygen (PO₂) and carbon dioxide (PCO₂). Chest X-ray and fibrobronchoscopy are also added to the final evaluation of lung suitability. If deemed suitable for transplantation, the lungs are flushed with preservation solution and cold stored on ice, ready to be used for transplantation.

While EVLP protocols all account for reperfusion, reconditioning, evaluation, and cooling periods, two main philosophies have been diversified over time, summarized in the Toronto and the Lund protocols. The main differences are shown in Table 29.2.

29.3 Clinical Application

Ex vivo lung perfusion technique is used to evaluate and/or recondition the function of lungs procured from marginal donors.

The prototypical use of EVLP for lung evaluation is in donation after cardiocirculatory determination of death (DCDD). When blood flow through the lung is absent, $\text{PaO}_2/\text{FiO}_2$ ratio, which is the main determinant of lung suitability for transplantation, cannot be assessed. EVLP allows to restore blood flow and render evaluation of the lungs possible. The first application of clinical EVLP was in fact to evaluate lungs in a case of donation after cardiocirculatory determination of death [16]. The donor was a patient dying of acute myocardial infarction in a cardiac intensive care unit after failed cardiopulmonary resuscitation. The concept of EVLP as an evaluation tool in DCD is of culprit importance, given the lack of organs and the need to explore new pools of lung donors. However, there might also be cases of donation after brain death determination (DBD) when lung function is doubtful. In these cases, EVLP may extend assessment comfort zone by improving the ability to perform a physiologic and objective evaluation of lung function. In this sense, EVLP has dramatically changed the scenario of organ suitability and procurement, as shown in the EVLP diagram flow that we adopted at our institution (Fig. 29.2).

EVLP also allows to recondition the function of previously rather normal donor lungs that worsened over the donation process to a point that rendered them

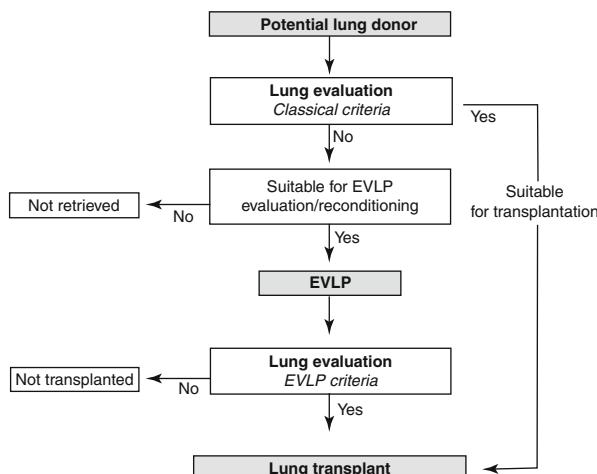


Fig. 29.2 Clinical EVLP diagram flow. The lungs offered for transplantation are first evaluated by the *classic criteria* (oxygenation, history of smoking, age, presence of secretions, chest X-ray): If they are deemed suitable, transplantation is performed. If the lungs do not satisfy the *classic criteria*, they may undergo EVLP after which a second organ evaluation is performed using the *EVLP criteria* (pulmonary arterial pressure, pulmonary vascular resistances, oxygenation, secretions, chest X-ray, surgeon's judgment). If, after EVLP treatment, the lungs are suitable, transplant is performed

unacceptable for transplantation. Deterioration over time of donor's lung function is much relevant; international data report that only 15–25 % of lungs from multi-organ donors are used for transplantation [6, 12]. In a recent report from the Nord Italia Transplant program (NITp), we observed a rate of lung donation of 29 % in a cohort of 201 potential lung donors [13]. In fact, low $\text{PaO}_2/\text{FiO}_2$, alteration on the chest X-ray, neurogenic inflammatory lung edema, inhalation injury, and complication related to the treatment in the intensive care unit (e.g., barotrauma and pulmonary edema) often occur in brain death multiorgan donors [2, 14, 19] and contribute to lung rejection. Ingemansson et al. were the first to show that lungs from DBD donors, previously rejected by other centers, could be safely transplanted after EVLP reconditioning [8]. This triggered a number of clinical applications of the technique (Table 29.1), fostered by the study of Cypel et al. that showed no inferiority of clinical transplantation of lungs retrieved from high-risk donors and reconditioned by EVLP [4].

Lung reconditioning has in fact a number of advantages: EVLP allows to dehydrate edematous lungs by the hyperoncotic solution used to perfuse the lung during the procedure. It allows to finely tune ischemia–reperfusion injury by gentle reperfusion and ventilation of the ischemic lungs. A thorough clearance of thrombi from the pulmonary vasculature is also an indirect benefit of EVLP. Optimization of ventilation during the procedure and at the time of cooling is of great importance for organ preservation. Finally, there might also be a preconditioning effect induced by the double cooling period that the EVLP lungs undergo.

Overall, provided evaluation and reconditioning often coexist, EVLP allows safer transplantation of the lungs from marginal donors.

29.4 Future Directions

We deem that the true potential of EVLP is to repair previously injured lungs.

The time frame of EVLP, potentially as long as 12 h [3], allows to repair diseased organs. In fact, gene, cellular, or pharmacological therapies may be applied during EVLP. Martins et al. have shown that the administration of adenoviral-mediated human IL-10 to the donor lung reduced ischemia–reperfusion injury and improved graft function after lung transplantation in a pig lung transplantation model; transfection prevented the release of inflammatory cytokines such as IL-6 in the lung tissue and plasma [11]. Lee et al. showed in an ex vivo perfused human lung injured by *E. coli* endotoxin that treatment with allogeneic human mesenchymal stem cells or the conditioned medium restored normal fluid balance [10]. We have documented that salbutamol reduces pulmonary artery pressure and improves respiratory mechanics during EVLP [17].

Many investigations on EVLP are ongoing. These will contribute to improve technical aspects of the procedure and will perhaps open new possibilities for EVLP. Overall, these efforts underline the breakthrough of organ reconditioning before transplantation.

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Part V

Monitoring the ECMO Patient

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30.1 Introduction

The daily care of an ECMO patient is a complex multidisciplinary task. As other critically ill patients, the ECMO-supported one must be re-evaluated for the primary disease that leads to ICU admission and for the possible development and treatment of other organ failures. The complex relationship between the patient and the ECMO circuit makes sometimes difficult to understand how the patient is doing. Other tasks refer to the monitoring of the ECMO circuit and the prevention of complications. Some other chapters in this book will address specifically some of the pitfalls in the management of these patients (complications, monitoring, ventilation); we will here focus on global daily care and its relationship with the ECMO equipment. The day of our ECMO patient will start with nursing care, followed by a careful head-to-toe assessment of organ functions to reveal actual problems and draw the daily care plan.

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30.2 Daily Nursing of the ECMO Patient

Daily nursing in the intensive care unit (ICU) is a fundamental therapeutic intervention, generally performed to improve patient hygiene, ameliorate patient comfort, prevent iatrogenic infections and assess skin integrity [1]. Patients in ECMO are generally unstable, and nursing care may be more challenging and hazardous due to the strict dependence of patient's oxygenation on the maintenance of ECMO blood flow, anticoagulation and possible decannulation. It consists in complete bed bath, oral hygiene and sheets and dressing replacement as in other ICU patients [2], with some precautions related to the risk of bleeding in anticoagulated patients and to the specific management of ECMO circuit.

During mouth care, trauma to the oral mucosa should be avoided with the use of swabs without or controlled low aspiration [3]; the position of the endotracheal tube should be changed two to three times in a day to preserve the oral mucosa and labial commissures; when fixing the ET tube, the commissures must be protected from the beginning interposing anti-decubitus dressing; the same applies to protect the nostrils in the case of nasotracheal or nasogastric tubes. If hairs need to be removed, an electrical razor is recommended.

Cannulation sites must be examined, as all the other catheters in place, to rule out signs of infection or bleeding; therefore, a transparent semipermeable dressing is preferred if there is no bleeding. Routine cannula dressing changes must follow the same rules stated by the Infectious Diseases Society of America (IDSA) guidelines [4]. When renewal of dressing is deemed necessary, it must be pulled off towards the insertion site to minimise the risk of cannula displacement. The distance between the insertion site and the end of the wire-wound cannula must be checked and recorded at the beginning of the nurse shift in order to recognise cannula dislodgement; at the same time the integrity of the cannula fixing system is checked (Fig. 30.1). The cannula and the tubing must be maintained along the leg axis for at least 40 cm in the femorofemoral veno-arterial (VA) or venovenous (VV) configuration; the skin in contact with the tubing must be protected; if an internal jugular cannula is in place, it should be fixed to the patient's head with a bandage. Never leave the weight of the ECMO tubing exerting traction to the cannula. Furthermore, during VA ECMO, frequent evaluation of peripheral pulses, skin temperature and colour should be performed to avoid lower limb ischaemia; in VV ECMO the efficacy of venous return from the distal leg and possible haematoma formation near the insertion site should be assessed by means of daily measurement of thigh circumference.

Mobilisation for back hygiene, sheets replacement and assessment of skin integrity may be performed either by logrolling the patient or by means of a scooping stretcher attached to a lift (Fig. 30.2), to minimise tube kinking and alteration in blood flow [3]. In our experience, daily nursing may be associated with several alterations of vital signs, such as tachycardia, hypertension and arterial desaturation (Fig. 30.3). These adverse events are mainly related to a neurovegetative response to stimuli, especially at the beginning of the procedures, during oral care and mobilisation; additional pulse sedation may be required to accomplish such nursing tasks.

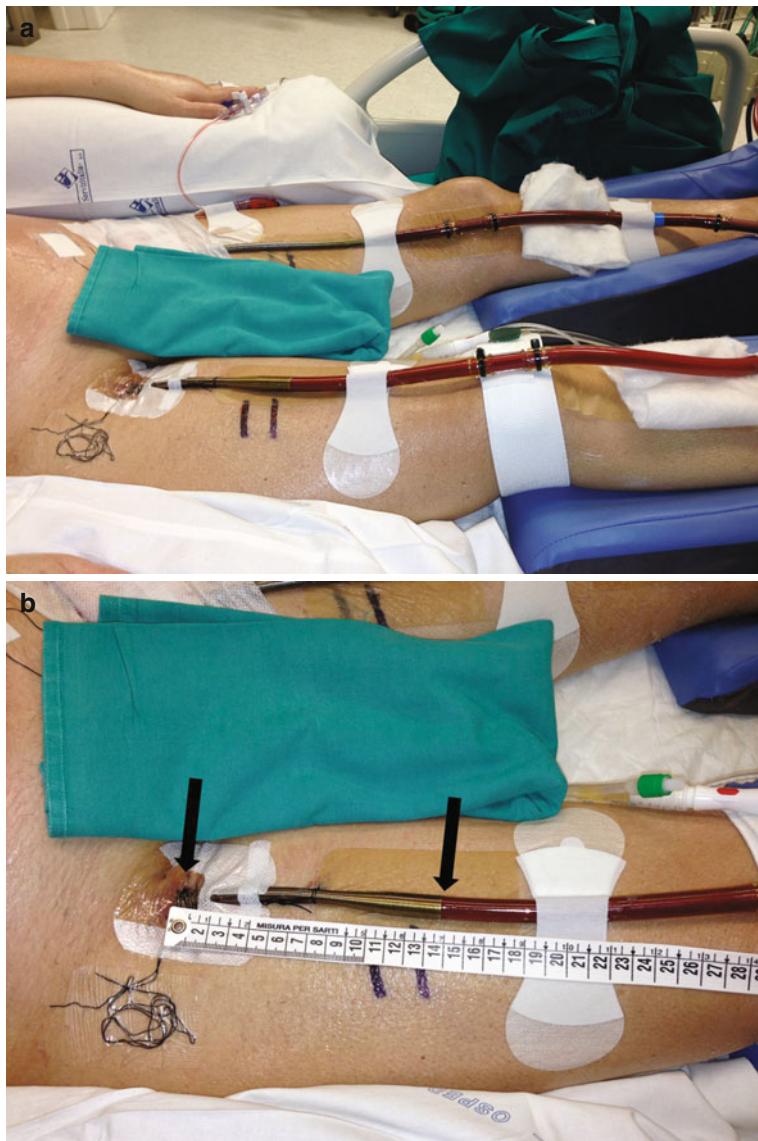


Fig. 30.1 ECMO cannulas' care. Panel (a): medication and fixation of the ECMO cannulas and tubing along the leg axis. Panel (b): measurements to assess cannula dislodgement

In relatively hypovolaemic patients, both elevation of the stretcher and mobilisation on the side may affect the position of the ECMO cannulas, mainly the drainage one, into the vessel with a reduction in effective ECMO blood flow and therefore desaturation.

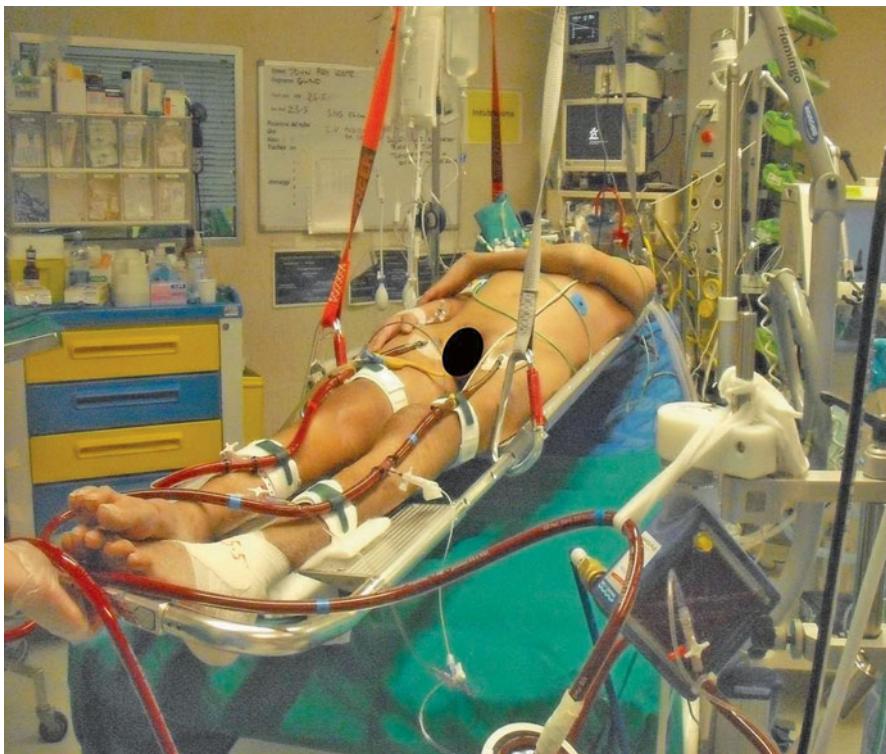


Fig. 30.2 Linen change with a scooping stretcher attached to a lift

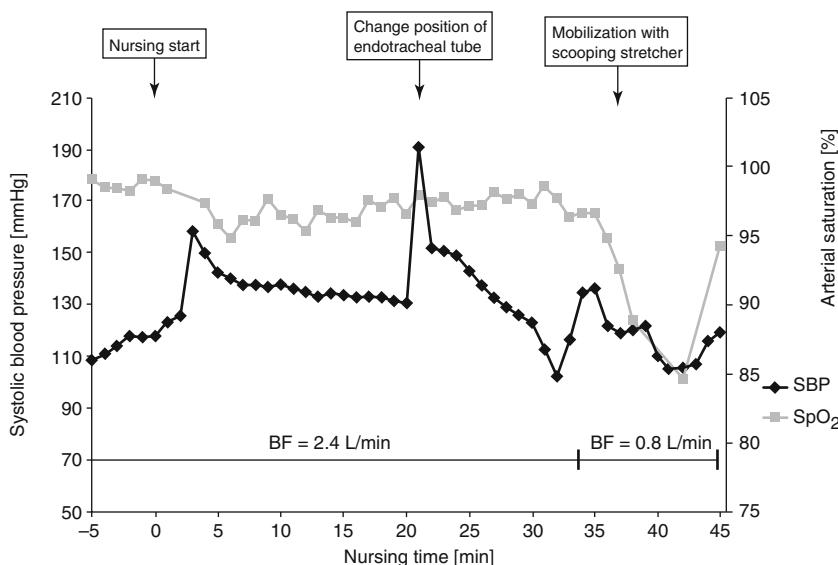


Fig. 30.3 Typical course of vital signs (*sBP* systolic blood pressure) and arterial oxygenation (*SpO₂* pulse oximeter saturation) during daily nursing care

Finally, when the patient is lightly sedated, as in the weaning phase, a brisk increase in the work of breathing can ensue during nursing care (elevation in respiratory rate and in minute ventilation); a higher level of ventilatory support may therefore be required during daily nursing.

Hence, we suggest that daily nursing should be performed by two or three nurses (at least one experienced in ECMO management) with an extra staff member designated to monitor tubing and circuit, ensuring there is no kinking or tension. It should only be undertaken when medical personnel are present or readily available to manage circuit problems, to administer additional sedation if deemed necessary or to adjust ventilatory support. It should be scheduled during the day shift, avoiding nocturnal turning unless essential [3]. Finally, if the patient is greatly unstable, for example, in ongoing active bleeding, daily nursing must be deferred or not be performed at all, according to clinical judgement.

30.3 Daily Assessment of the ECMO Patient

Physicians and nurses will evaluate completely the patient at least three times in a day. A head-to-toe approach is applied for simplification.

30.3.1 Head and Sedation

We know that it is possible, with the new ECMO technology, to have a patient walking around while on ECMO support (see sect. 30.5), but heavy sedation, and sometimes muscle paralysis, is needed in the most critical one, as a tool to decrease oxygen consumption (VO_2) and therefore improve global oxygenation. In these cases, adequacy of sedation is difficult to evaluate; vital signs (heart rate and systemic arterial pressure) plus objective measures of brain function, such as bispectral index (BIS), are recommended in the recent published guidelines [5].

Critically ill patients receiving ECMO have been reported to have increased sedation requirements; the literature is mainly related to neonatal and paediatric patients; scanty data are available for the adult one [6]. The possible interference of artificial oxygenators with some sedative and analgesic drugs has also been reported [7–9], and two studies to understand the pharmacokinetics of antibiotics, sedatives and analgesics during ECMO are under way [10, 11].

To have a calm and cooperative patient is a very difficult task. Due to the safety concerns about possible cannula dislodgments and even decannulations, agitation and delirium must be promptly treated. Never leave the lightly sedated, apparently calm patient unattended, especially during the night shifts: A brisk arousal or a nightmare can result in a disaster.

The pupils' reactivity is our “neurological window” in the sedated and paralysed patient and must be evaluated several times during the day, since the rate of neurological complications (stroke and bleeding) is still relatively high ranging from 4 to 9 % in the most recent series [12, 13].

30.3.2 Airways and Ventilation

As stated above the oral or nasal endotracheal tubes carry a high risk of mucosal bleeding; if the ECMO run is prolonged, a tracheostomy must be planned for patient comfort and as a weaning facilitator [14]. Percutaneous techniques are preferred over the surgical ones; having an otolaryngologist specialist involved can assure surgical assistance if a bleeding problem will ensue in the following days. As for other planned surgical procedure, anticoagulation is withheld 4–6 h before and after the procedure, and platelets are transfused as needed; strict monitoring of ECMO circuit for clot formation is performed; and if necessary, the ECMO circuit will be changed.

Several questions need to be answered daily during the ECMO run:

- ***Is the ventilatory setting “protective”?***

This question is surely the principal one at the beginning of the ECMO course, but it remains valid for every day thereafter. Keep in mind that spontaneous breathing with huge transpulmonary pressure swings carries the hidden danger of harming the lung, mainly if pursued too early in the setting of increased capillary leak. On the other side, maintaining the patient for an unnecessary prolonged time heavily sedated and even paralysed carries the risk of diaphragmatic dysfunction and polyneuropathy. What we have considered as “lung rest ventilatory settings” is of debate; Extracorporeal Life Support Organization (ELSO) guidelines [15] give targets of PEEP, peak airway pressure and respiratory rate (PEEP 10 cmH₂O, PIP 20 cmH₂O, RR 5–10), that are very difficult to achieve, in our experience, in the early phases when capillary leak is an issue, due to frothy oedema coming up in the endotracheal tube and drowning the patients. Also other ECMO centres would decrease PEEP with caution only when the high permeability acute phase subsides and in the absence of alveolar bleeding [3, 16, 17]. If respiratory acidosis is an issue, it must be corrected slowly to avoid brisk changes in acid–base balance and its deleterious effect on cerebral circulation [15].

- ***Can the patient start a weaning process leading to ECMO disconnection?***

We need to evaluate every day the possibility of weaning the patient from ECMO support. In VA ECMO, a key role in the weaning decision is played by daily echocardiographic evaluation of the patient's heart function during trials of ECMO blood flow decrease [18–20] (see Chap. 18). In the respiratory patient in VV ECMO, we need to evaluate if gas exchange and respiratory mechanics will allow weaning. Improvement in oxygenation through the natural lung is easy to assess if the principles of O₂ delivery are applied to the patient-ECMO relationship, partitioning the relative contribution of natural and artificial lung to oxygenation. We like to monitor the ECMO patient with a pulmonary artery catheter, and therefore we can evaluate shunt fraction and the contribution of the natural lung to VO₂ by simply drawing blood gases from the arterial and pulmonary artery catheter and the contribution of ECMO by drawing blood gases from the inlet and outlet of the artificial lung. The real challenge is to evaluate the ventilatory endurance of the patient and to understand if the ventilatory burden can be accomplished without

ECMO. This process normally takes some days or even weeks. If there are important bleeding complications that put the patients at risk of death and ECMO disconnection is warranted, we must indeed evaluate if we can handle gas exchange with “protective” settings also in controlled mechanical ventilation.

- **Are there complications?**

Huge pleural effusions are not characteristic of ARDS at the beginning but can develop during the ECMO run due to fluid overload or a decompensating heart function. In these cases we must evaluate the introduction of forced diuresis or even CRRT or add inotropes before attempting a thoracentesis, because this manoeuvre can lead to a haemothorax in the ECMO anticoagulated patient.

The same reasoning applies to pneumothorax. The ELSO guidelines [15] suggest that a conservative approach must be implemented even for pneumothoraces up to 50 %, without haemodynamic compromise and not enlarging, due to the high bleeding complications related to chest tubes placement, often leading to thoracotomies [21–23]. Lung ultrasound and chest x-rays are used to monitor the pneumothorax, while an important reduction of airway pressure is attempted with an increase in ECMO blood flow to support oxygenation [24] (Fig. 30.4).

- **Is gas exchange deteriorating?**

Oxygen desaturation can be patient or ECMO equipment related. First, as a temporary manoeuvre, increase the ventilator and ECMO FiO_2 to 100 %. If the patient is in full ECMO support and the native lung is not participating in gas exchange, carefully check the ECMO equipment: Is blood flow decreased? Is the oxygen supply to the artificial lung ok? Is the outlet blood bright red and significantly different from the inlet blood?

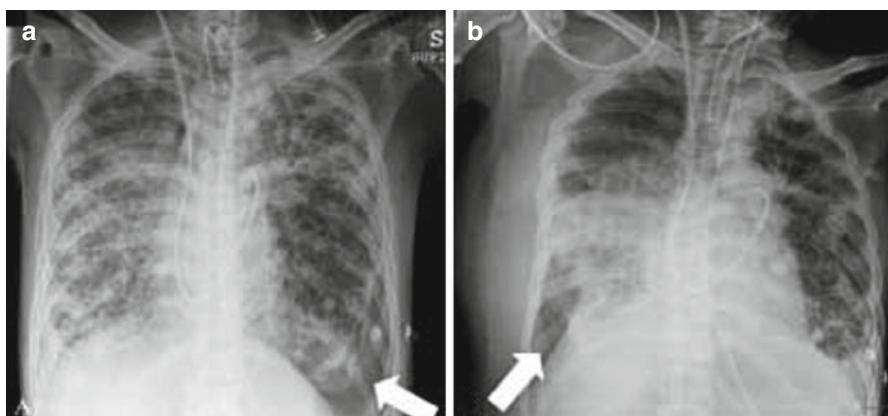


Fig. 30.4 Bilateral pneumothorax in a patient with severe pulmonary tuberculosis. Chest x-rays showing left (panel a) and right (panel b) spontaneous pneumothorax. Both were left undrained and ventilation pressures were decreased while oxygenation was guaranteed by extracorporeal membrane oxygenation (ECMO). The patient eventually survived. Arrows indicate air presence in the pleural spaces (Reprinted by permission of Edizioni Minerva Medica from Mauri et al. [24])

If the native lung is consistently participating in gas exchange, we must assess the patient and the ventilator: Is chest expansion normal, with bilateral respiratory sound? Are there airway secretions with increased peak inspiratory pressures? Is there a ventilator malfunction? Is the patient's metabolic demand increased? We must also evaluate the haemodynamics of the patient, since oxygen desaturation can ensue from an increased cardiac output with a proportional decreased contribution of ECMO to oxygenation.

30.3.3 Haemodynamic and Volume Status

Assessing volume status can be challenging in ECMO patients and is affected by cannula position. In the VV femorofemoral approach, central haemodynamics is not really disturbed by the ECMO circuit, and we like to monitor it with a pulmonary artery catheter since it gives us tools to fully understand the gas exchange of the patient and gives information about pulmonary hypertension. Central venous pressure and pulmonary capillary pressure in association with echocardiography can help to evaluate the volume status of the patient. Another parameter to follow is the negative pressure in the drainage cannula; if relative hypovolaemia will ensue, sometimes the first sign will be "chattering" of the drainage line due to collapse of the inferior vena cava around the cannula. Cardiac output by thermodilution has known limitations [25], but the trends are still important to follow. If the drainage cannula is in the right atrium, we use the ventricular port as injection site for cardiac output measurements [26].

On VV ECMO, central venous saturation (SvCO_2) is contaminated by arterialisated blood coming from the artificial lung and therefore cannot be used to assess the adequacy of cardiac output to metabolic needs. The saturation of blood at the inlet of the artificial lung can be monitored indeed, low saturation being surely a sign of hypoperfusion.

Pulmonary hypertension is quite common in patients with ARDS treated in ECMO, and we need to understand its relationship with cardiac output, oxygenation and CO_2 . A fixed pulmonary artery pressure increasing over days is a poor prognostic factor. Echocardiography and continuous monitoring through a pulmonary artery catheter are our tools to assess if right ventricular failure is in development and the needs for some specific treatments (inhaled nitric oxide, sildenafil, bosentan).

30.3.4 Infection Evaluation and Workup

If the cause of ARDS was infective, we need to evaluate its resolution and recognise if new infections are ensuing. We know that the risk of infection is high in the ECMO patient and is mainly related to the length of the ECMO run, patient's age, VA access and immunosuppression [27–31]. Diagnosis of a new infection can be difficult since some of the clinical clues we normally use in other ICU patients can be affected by the presence of ECMO [32]. The inflammatory response of the patient to the ECMO foreign surfaces can influence white blood cell count, and chest x-ray is almost never diagnostic of a new infiltrate in the setting of ARDS. The ECMO heater controls

the patient's body temperature, and fever response is therefore blunted; the feverish patient on ECMO must face the cooling effect of the ECMO circuit, and this will result in high oxygen demands. The suspicion of a new infection should arise from small signals, like a difference between patient's and ECMO temperature of 0.3–0.5 °C, presence of mottled skin and purulent secretions and variations in haemodynamics, which need to be integrated with biomarkers of infection like C-reactive protein and procalcitonin [33]. The most common infections during ECMO runs are secondary VAP and bacteraemia. We monitor the colonisation of the airways with surveillance cultures drawn at least once in a week, also if their role is controversial. Colonisation with MDR microorganism by rectal swabs will be searched if the patient has been in the ICU for more than 15 days. If a new infection is suspected (purulent secretions, brisk increase in biomarkers with hyperdynamic haemodynamics, etc.), blood cultures and other specimens will be sent, and the antimicrobial therapy will be changed empirically and then adjusted on microbiological results. An “infectious disease task force” was established by ELSO in 2008 to address issues on diagnosis, treatment and prevention of infections during ECMO. They concluded that there is no reason for antibiotic prophylaxis solely for ECMO after the initial bolus at cannulation and remarked on the importance of infection prevention (hand washing, no circuit break, limiting manipulation of the ECMO circuit and other catheters, head of bed elevation, oral hygiene and decontamination) [32, 34].

30.3.5 The Abdomen and Nutrition

The abdomen must be evaluated for liver and splenic enlargement and bowel function. Liver enlargement is quite common in these patients as the result of stasis but can become a real problem with the development of secondary hepatic insufficiency in cases of severe right ventricular failure; in such cases decompression of the right ventricle can be necessary.

Abdominal compartment syndrome (ACS) has been described in the adult ECMO literature [35, 36], mainly in the veno-arterial mode, as a result of fluid overload. In our experience another possible cause is spontaneous retroperitoneal bleeding (Fig. 30.5). Measurements of intra-abdominal pressure are therefore recommended. The development of ACS in both VA and VV femorofemoral approaches will compromise the ECMO blood flow, and a new drainage cannula must be inserted in the jugular vein. Surgical decompression can be needed if bowel, renal and respiratory compromise is ensuing.

Early in 1983, Iapichino and co-workers pointed out that effective nutritional support could be provided safely to patients undergoing ECMO, even if the patients are heavily anaesthetised and curarised [37]. The same findings have been reported by other ECMO centres [38–40]. The data on nutritional requirement and tolerance are scanty in the adult ECMO population [41], and the Australian and New Zealand Intensive Care Research Centre already started a survey to answer some question about this topic [42].

In our experience the tolerance to enteral feeding is good also in the most severe ARDS patients since the beginning. We needed to shift to parenteral nutrition only

Fig. 30.5 Abdominal compartment syndrome due to a spontaneous lumbar haematoma in a patient on VV ECMO



in few cases due to important gastric bleeding or development of abdominal compartment syndrome. Severe diarrhoea can be a problem mainly in the femorofemoral ECMO, due to the possible faecal contamination of access sites. Faecal management devices must be avoided or kept in place for a very short time due to the high risk of rectal lesions in these patients. In these cases, changing the diet or decreasing the velocity of enteral nutrition by adding a parenteral integration can be the right choice.

30.3.6 Hepatic and Renal Function

Hepatic and renal functions must be carefully evaluated and monitored since these have been demonstrated to be related to a poor prognosis [13]. Liver function can be impaired for many reasons (overwhelming sepsis, medications, cardiogenic shock, right ventricular failure, haemolysis); the treatment of the primary insult is almost always the cure. In few cases extracorporeal liver support (MARS) [43] or plasma exchange or adsorption (CPFA) can be of value.

Severe renal impairment must be treated with continuous renal replacement therapies (CRRT) early in its course due to the risk of fluid overload. If the patient on ECMO requires a CRRT system, some key points must be taken into account [13]:

1. The CRRT circuit can be kept independent from the ECMO one by inserting a new dialysis catheter. If this is the choice, the risk associated with a new catheter placement in a fully anticoagulated patient must be faced.
2. If the CRRT system is connected to the ECMO circuit:
 - a. You must know the pressures' regimen inside the ECMO circuit and the pressure alarms, both inflow and outflow, that will stop the CRRT machine. In some CRRT systems the alarms can be changed to allow the connection to the ECMO circuit.
 - b. Try to avoid the negative pressure compartment of the ECMO circuit, i.e. the drainage line from the skin insertion to the centrifugal pump head. The risk of air entrance in the ECMO circuit during CRRT manipulation is higher in the negative pressure drainage line.
 - c. The CRRT machine can be connected to the side-ports across the artificial lung used for monitoring the pressure drop (resistance) and withdrawing blood gases to assess artificial lung performance. The post-pump pre-oxygenator port and the post-oxygenator port are both at positive pressure; both sides can be used as inlet and outlet for the CRRT system, if this allows positive pressure on both inflow and outflow lines. If the CRRT system in use would not allow positive pressure in the inlet, some resistance to the inflow line can be added but this will increase the risk of clotting and haemolysis.
 - d. We prefer to connect the inflow line of the CRRT machine to the post-oxygenator port and the outflow line to the pre-oxygenator one (post-pre configuration). In this way a recirculation of oxygenated blood will result but the high efficiency of the oxygenator would accomplish for it. We think this is safer than having a shunted venous blood, as it will be the case if the inflow of the CRRT will be attached to the pre-oxygenator and the outflow to the post-oxygenator port. With the post-pre configuration, the oxygenator will also act as an additional bubble-trap if air would enter the CRRT circuit.
 - e. The CRRT system can increase the heparin requirements. Regional anticoagulation with sodium citrate can be used in the CRRT machine while the patient is maintained anticoagulated with heparin, or with other anticoagulants if heparin induced thrombocytopenia (HIT) is an issue.

30.3.7 Bleeding Management and Transfusion Targets

Critically ill patients normally develop anaemia after 3 days of ICU stay. The ARDS patient on ECMO needs to have a good haematocrit level to maintain good oxygen-carrying capacity and delivery. High volumes of blood, ranging between 70 and 100 mL/day, are drawn every day to monitor blood gases (patient and ECMO), coagulation and routine biochemistry; therefore, the normal transfusion requirement is 1 PRBC every 2 days. If bleeding will ensue, the transfusion requirements will increase dramatically, and this will impact the prognosis of our ECMO patient [44, 45].

In order to prevent bleeding complications, a “do no harm” approach must be used: no intramuscular or subcutaneous shots, no thoracentesis, no chest tubes and no changes of nasogastric or urinary catheters.

Bleeding can be localised or generalised. In the first case manoeuvres at the bleeding sites, like compressive gauzes on cannula insertion site or packing of nasal or oral cavities, can per se be effective. If bleeding is generalised and persists also after temporary heparin discontinuation, thromboelastography can be used in addition to normal coagulation assay, to understand if there is an underlying pathological derangement in coagulation. In case of major haemorrhages, a massive transfusion protocol must be followed trying to transfuse matched components (PRBC, FFP, platelets, fibrinogen, tranexamic acid). Surgeons or interventional radiologists must be involved early and useful imaging gathered [46]. If heparin is stopped, a strict monitoring of the ECMO circuit for clots and increase in drop pressure across the artificial membrane must be implemented.

30.4 Imaging in ECMO Patients

Chest x-rays and ultrasounds are our routine bedside imaging in the ECMO patient [47]. They provide a lot of information and only in few cases we need other special imaging. A CT-scan study can become necessary when we are searching for an occult haemorrhage or an infection source and, if the ECMO course of the patient is prolonged, to assess the evolution of lung parenchyma [48]. The transport of the patient on ECMO outside the ICU is demanding but can be safely accomplished with a careful ICU preparation (see chap. 39); therefore, we can weigh the risk of transportation and the benefit we aspect from the study.

30.5 Physical Therapy and Mobilisation

Muscle dysfunction is common in patients in the intensive care unit (ICU) due to inactivity, inflammation, use of pharmacologic agents (corticosteroids, muscle relaxants, neuromuscular blockers, antibiotics) and the presence of neuromuscular syndromes associated with critical illness [49–51]. Hence, it is important to prevent or attenuate muscle deconditioning as early as possible in patients with expected prolonged bed rest, and appropriate interventions (passive or active physiotherapy, mobilisation or walking) should be chosen according to clinical conditions [52]. There are several reports in the literature on active physiotherapy and walking during ECMO [53–59] which mainly refer to patients candidate to lung transplantation; in this specific category of patients, physiotherapy allows a better conditioning for transplantation, resulting in a reduction in mechanical ventilation (MV) days after transplantation and in higher survival rates compared to those on MV [53]. Ambulatory ECMO and active physiotherapy require jugular cannulation with a double-lumen cannula, which allows an easier management during the manoeuvre. However, according to the European Society of Intensive Care Medicine (ESICM) recommendations [52], active physiotherapy should

not be performed in patients with haemodynamic instability, high FiO₂ or high levels of ventilatory support; hence, despite the published promising results, physiotherapy in the acute severe ARDS patients on ECMO should be carefully evaluated. Major concerns are related to the risk of bleeding or decannulation during the manoeuvres and to the inability of patients to tolerate physical efforts that may lead to non-protective ventilation, sustained cough and bronchial bleeding or haemodynamic failure. Thus, in acute ARDS patients, especially in those with femoral cannulation, physical therapy should consist of mobilisation of the upper limbs progressively implemented in the last part of respiratory weaning and fully performed only after ECMO disconnection.

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31.1 Introduction

After worldwide successes with ECMO for the 2009 pandemic influenza H1N1 [1, 2], and publication of the results of the *Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure* trial that showed a survival advantage for ECMO over conventional ventilator management for severe respiratory failure [3], there has been renewed enthusiasm for venovenous ECMO (VV ECMO) for pulmonary support. Similarly, venoarterial ECMO (VA ECMO) for acute cardiogenic shock is also becoming a more commonly used tool in the early management of critically ill patients as part of a treatment strategy to bridge to recovery, ventricular assist device implantation, or transplantation. Algorithms that incorporate early VA ECMO as part of the treatment for witnessed cardiopulmonary arrest (ECMO-assisted cardiopulmonary resuscitation) are also becoming more common and have resulted in a twofold increase in neurologically intact patients surviving to discharge [4] (Table 31.1).

At the same time, the intensivist has become more familiar with echocardiography and ultrasound techniques even outside the traditional field of cardiac surgery, making it possible an “ultrasound-guided approach” to the indication, correct positioning, and patient monitoring during extracorporeal assistance. The targets of ultrasound monitoring during extracorporeal circulation will be different depending

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Table 31.1 Common indications and purposes of venoarterial ECMO

Common indications
Cardiogenic shock
Refractory cardiac arrest
Impossible weaning from cardiopulmonary bypass during cardiac surgery
Myocarditis
Intoxication or sepsis with severe myocardial depression
“Primary graft failure” after heart or lung transplant
Purposes of extracorporeal support
“Bridge to recovery” – assistance until recovery and weaning from support
“Bridge to bridge” – until the implantation of medium- or long-term mechanical support (VADs)
“Bridge to transplant” – until heart transplant
“Bridge to decision” – to evaluate the possible cardiac recovery and the most appropriate therapy

on which approach (VV versus VA) has been used. During circulatory assistance, after the patient has been selected and the cannulation sites have been evaluated, the attention will be focused on the correct functioning of the mechanical support (position of the cannulae, thrombus formation, etc.) and on the cardiac function, monitoring its recovery and deciding when the patient is ready to be disconnected from support. During respiratory support, after assessing the proper positioning of the cannulae, it is important to evaluate the cardiocirculatory status of the patient before and during the assistance.

The echocardiographic approach, transthoracic (TTE) versus transesophageal (TEE), will depend on the patient's characteristics (acoustic windows and echogenicity) and on the region of the heart and vessels of interest. Ultrasound monitoring during ECMO is not only important for cardiac evaluation but also for choosing the best sites for cannulation (especially during percutaneous procedures) and for monitoring the peripheral perfusion of the cannulated limbs.

Despite its important role in the management of critically ill patients, there are few published data outlining the use and experience of echocardiography and ultrasound in critically ill adults requiring extracorporeal support. Because ECMO is based on the principles of oxygenation and hemodynamic support via blood flow within large-bore cannulas placed in or near the heart in patients with cardiorespiratory failure, echocardiography would be expected to have a fundamental role throughout the care of patients supported on ECMO. In this chapter, we outline the targets and the modalities of ultrasound evaluation in patients requiring extracorporeal assistance.

31.2 Venoarterial ECMO

As pointed out in the previous paragraph, the primary aim of VA ECMO is to support the circulatory function in patients with cardiac failure (acute or chronic, acutely decompensated) of different etiologies. Besides this traditional indication, in the last decade, venoarterial ECMO has emerged as a circulatory and respiratory support for refractory cardiac arrest, allowing diagnostic evaluation and treatment in selected patients that would have a mortality rate close to 100 %.

Compared to other mechanical cardiac assistance devices, ECMO has the advantage of reduced costs, and the possibility of being easily and rapidly instituted outside the operating room (critical care units, cardiac catheterization suites, or emergency departments) even during cardiopulmonary resuscitation maneuvers. It also has limitations: it is a short-term support, with important infectious, thrombotic, and hemorrhagic complications, and causes an increase in the left ventricle afterload.

In the next paragraphs, we are going to analyze in details how a comprehensive ultrasound evaluation should be performed during the different phases of ECMO support. For cannulation procedures, we refer to the peripheral cannulation, which is employed in the majority of patients. Central cannulation (right atrium to ascending aorta) represents a specific condition, reserved almost exclusively to the intraoperative cardiac surgery period (impossible weaning from extracorporeal circulation). In these cases, the ultrasound evaluation is represented by the intraoperative transesophageal examination performed to assist the weaning from cardiopulmonary bypass.

31.3 Indications to VA ECMO Support

31.3.1 Cardiogenic Shock

Patients with cardiogenic shock should be carefully evaluated: A comprehensive clinical history and examination together with a complete echocardiographic exam are necessary to determine their functional status as well as the presence of clinical conditions which can contraindicate the positioning of a circulatory assistance (Table 31.2). Echocardiography helps to exclude new reversible pathologies, which

Table 31.2 Contraindications to ECMO support

General
Severe, not reversible cardiac insufficiency with no indication to transplant or VAD as destination therapy
Severe, not reversible neurological injury
Terminal malignancy
Intracranial bleeding
Age ^a
Venoarterial ECMO
Aortic dissection
Severe aortic valve regurgitation
Not witnessed cardiac arrest
Prolonged CPR ^b
Venovenous ECMO
Cardiac arrest
Cardiogenic shock
Severe pulmonary hypertension

^aThe age limit is not uniform in different centers. It is usually considered “excessive” to assist patients older than 80 years old, even if the results are not significantly worse in this subpopulation

^bAlso the duration of CPR in patients supported for refractory cardiac arrest is not uniform in various protocols. In our center, the time limit is 45 minutes, but limits of 90 minutes are also reported in literature

may account for a patient's hemodynamic instability (such as cardiac tamponade, undiagnosed cardiac valve pathology, and LV dysfunction), avoiding the need for ECMO support. During the exam, it is important to study both the systolic and the diastolic function of the left ventricle, the function and dimensions of right ventricle, the valves (searching for functional or anatomic anomalies), and the pericardium, focusing the attention to the presence of pericardial effusion. It is of utmost importance to accurately evaluate the aortic valve and the aorta (ascending and descending): The presence of severe aortic valve regurgitation may have a detrimental impact on left ventricle unloading once a VA ECMO (in which LV afterload is increased) is positioned, and the detection of an aortic dissection is an absolute contraindication for VA ECMO positioning. The positioning of a venous cannula in the right atrium also dictates that right-heart anatomy be evaluated for any structural abnormality that may adversely affect the function and positioning of the cannula. Notable findings include a prominent patent foramen ovale, atrial septal defect, interatrial septal aneurysm, prominent Chiari network, presence of a pacemaker or implantable cardioverter-defibrillator leads, and tricuspid valve pathology (such as tricuspid stenosis or a tricuspid valve replacement).

31.3.2 Refractory Cardiac Arrest (Fig. 31.1)

The criteria to establish the indication for ECMO assistance in patients with cardiac arrest are primarily based on the clinical history and on the timing of CPR start (i.e., the duration of no-flow or non-assisted circulatory arrest) (Table 31.2). In this category of patients, the echocardiographic evaluation is limited to the anatomic aspects of cardiac chambers and valves, the study of cardiac function being impossible. In PEA (pulseless electrical activity) patients, it is important to distinguish a true PEA



Fig. 31.1 ECMO cannulae positioning during CPR

(the heart has no contractions, “electromechanical dissociation”) from a pseudo-PEA (the heart has contractions which are not sufficient to generate a significant pulse because of a severe dysfunction or extrinsic compression). Especially in these patients, it is important to look for clear and gross anomalies which can explain the cause of the arrest (the 4 Hs and 4 Ts of the ALS algorithm) focusing the attention on the dimension of the cardiac chambers – especially of the right ventricle to exclude pulmonary embolism – and on the presence of significant pericardial effusion. It is also possible to evaluate the efficacy of the thoracic compressions estimating the transaortic or transpulmonary flow. In these patients, it is also important to exclude clinical conditions – aortic dissection in primis – which contraindicate cannulation.

31.4 Cannulation

Ultrasounds also have a key role during ECMO cannulation, as they assist in the correct placement of ECMO cannulas. The evaluation of arterial and venous vessels is important for choosing the best site for cannulation. With ultrasounds, it is possible to determine the position of the veins and arteries, the potential anatomical variants, as well as the presence of significant pathologies of the venous (thrombosis) or arterial system (occlusion, significant stenosis, aneurysms, atheromas). If a significant pathology is found in the examined vessels, alternative sites can be evaluated to determine the most appropriate for cannulation. This aspect has to be investigated as quickly as possible, especially in cardiac arrest patients.

The evaluation of vessels size, especially of the arteries, is important for choosing the dimension of the cannulae; the size of the arterial cannula is the major determinant of the maximal output achievable with ECMO support, as larger cannulae permit a greater output. In our experience with adult patients, it is possible to achieve a total circulatory assistance with cannulae ranging from 15 to 19 French depending on the size of the patient. It is easy to obtain the approximate dimensions of the cannula in millimeters, dividing the size in French by 3. From this calculation, it is clear that we can safely cannulate arteries with a diameter greater than 5–5.5 mm. The ultrasound examination of the artery we intend to cannulate can tell if its diameter is sufficient to accommodate the smallest cannula able to provide an adequate blood flow to the patient. The presence of a vessel that is close in size to the cannula dimension warrants the positioning of a peripheral reperfusion cannula to prevent ischemia of the cannulated limb.

When commencing cannulation, guidewires are initially inserted percutaneously and positioned within the heart or great vessels, before the advancement of cannulas over these wires. Because of the strong echocardiographic artifacts that can be generated from these wires and cannulas, close attention must be paid to their placement.

In peripheral VA ECMO, the venous cannula is optimally located in the mid right atrium to provide unobstructed flow of central venous blood into the circuit. Transesophageal echocardiography (TEE) is useful to guide positioning. The return cannula is usually placed in the contralateral femoral artery and the tip located in the iliac artery or abdominal aorta. This region cannot be visualized with TEE. However,

imaging for placement of this cannula is usually not required. TEE can confirm that the guidewire used in percutaneous arterial cannulation is in the lumen of the aorta before dilatation, reducing the risk for extra-arterial cannula placement.

31.5 Monitoring ECMO Support

During ECMO support, the echographic evaluation – performed at least on a daily basis – is of utmost importance for the study of cardiac function as well as for monitoring the assistance and managing the complications. All these aspects are investigated during all the period of assistance that can be divided into three stages: the initial phase after connection, the intermediate of maintaining support, and the final of weaning and de-connection.

31.5.1 Initial Stage (After Connection)

After ECMO connection and the beginning of assistance, it is important to verify if the venous drainage is sufficient to maintain an adequate cardiac index. If it is not, echocardiography can help identifying the causes and verifying the efficacy of corrective maneuvers: It is possible to identify hypovolemia and resolve it, check the correct positioning of the cannulae, and detect masses (especially clots) which can obstruct the venous drainage (Fig. 31.2). In case of low-flow states during ECMO, it is also important to rule out problems to the arterial side of the circuit, for example, aortic dissection (not detected during pre-assistance evaluation or iatrogenic after-cannulation) or severe aortic regurgitation.

In patients who need ECMO support for refractory cardiac arrest, it is possible to perform the first cardiac evaluation soon after the beginning of the assistance to evaluate the recovery of mechanical activity that can take place spontaneously or after therapeutic interventions (revascularization, evacuation of pericardial effusion, surgical, or pharmacological resolution of pulmonary embolism). At this stage, it is also possible to detect possible abnormalities in contractility or significant valvular defects.

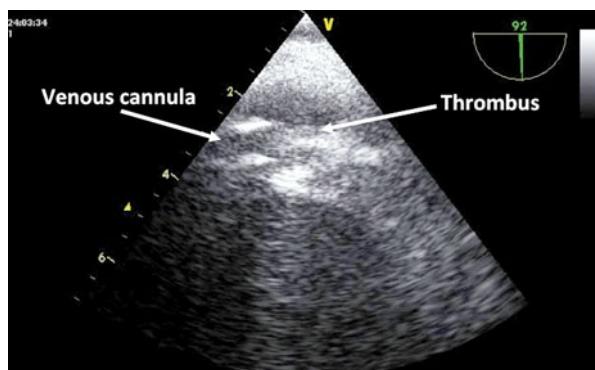


Fig. 31.2 Drainage cannula completely obstructed by a right atrial thrombus

31.5.2 Intermediate Stage (Maintaining Support)

The duration of the assistance is variable and depends on the initial causes that indicated it. ECMO support can be needed for few hours or days (e.g., in cases of arrhythmic cardiac arrest, accidental hypothermia, intoxications) or for considerably longer periods in some other cases (e.g., for myocarditis or for patients being bridged to long-term ventricular assistance device or transplantation).

The echocardiographic evaluation is essential during the subsequent days or weeks not only to monitor the recovery of cardiac function but also to avoid and treat potential problems and complications inherent to the mechanical assistance itself.

Together with the constant monitoring of global and segmentary contractility, it is important to verify the adequate drainage of the cardiac chambers and avoid their distention, particularly of the left ventricle. During peripheral VA ECMO, LV preload usually decreases (because of decreased pulmonary blood flow), but LV afterload increases (because of the pressurized return of blood via the arterial return cannula). In cases of very severe LV dysfunction, especially when associated with severe mitral regurgitation, the left ventricle may become more distended, and the aortic valve may not open. This will be indicated by a loss of pulsatility on the arterial pressure waveform. This can lead to stasis and thrombosis in the ascending aorta, LV cavity, and pulmonary veins and finally to problems to the mechanical assistance itself and to its weaning together with a very high embolic risk (Figs. 31.3 and 31.4). Echocardiographic aspects are the following: a dilated and impaired left ventricle, minimal aortic valve opening, severe spontaneous echo contrast in the ascending aorta, and severe mitral regurgitation. Failure of the aortic valve to open during peripheral VA ECMO support is a significant concern. In this situation, anticoagulation is increased and afterload is decreased while optimizing native LV output (by reducing ECMO flows and judicious use of inodilators) to facilitate aortic valve opening and resolution of spontaneous echo contrast in the left ventricle.

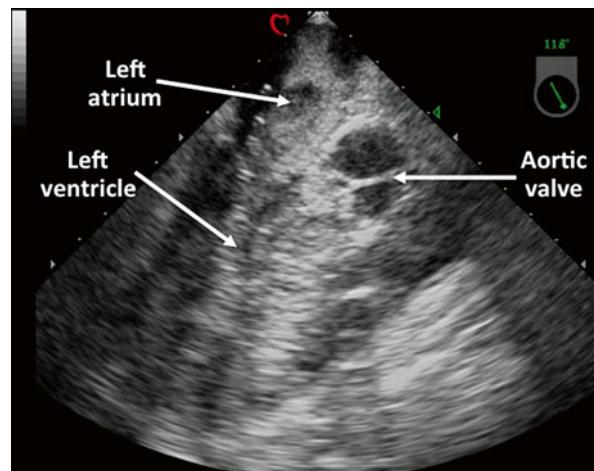
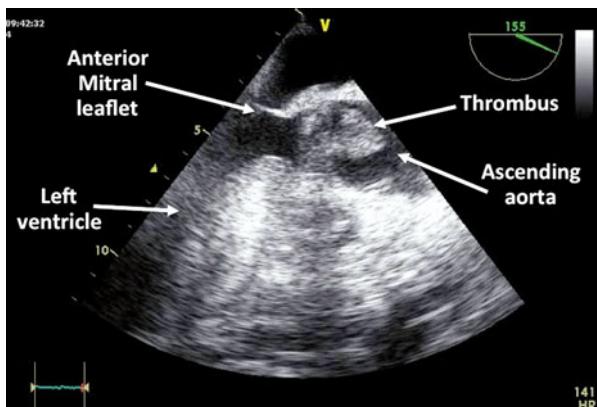


Fig. 31.3 Complete thrombosis of the left ventricle

Fig. 31.4 Thrombus in the ascending aorta, adherent to the left coronary aortic cusp



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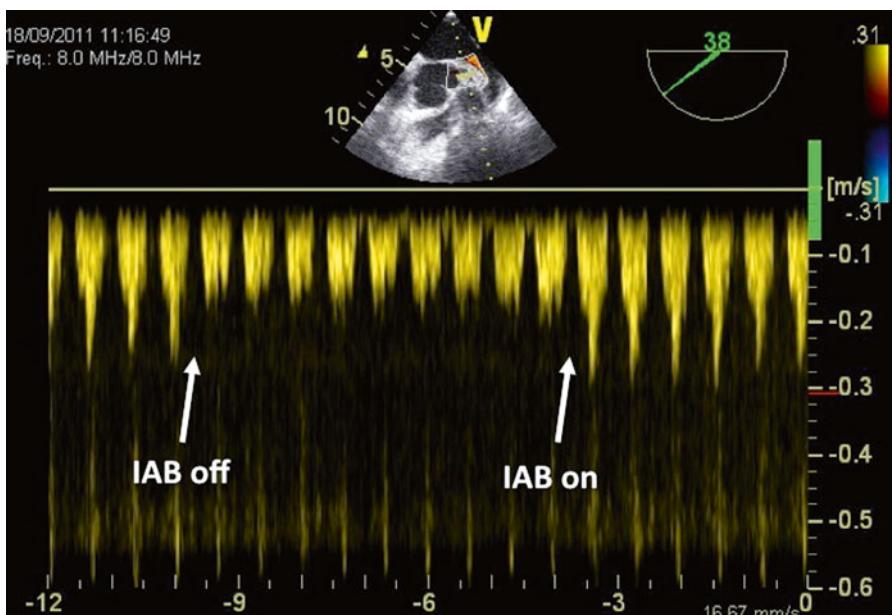


Fig. 31.5 Flow variation sampled at the left main left coronary artery when IABP support is suspended

Our strategy of “cardiac rest” is based upon the use of low-dose inotropes (e.g., dobutamine) to permit a constant opening and closure of the cardiac valves, together with aortic counterpulsation when it is not contraindicated. The echocardiographic control has a pivotal role in monitoring the cardiac rest; the use of aortic counterpulsation during ECMO support with peripheral cannulation is controversial, and strong evidences to support or discourage it are lacking. In our experience, we found a better left ventricle unloading, a preserved pulsatility to ECMO blood flow, and a positive effect on coronary, splanchnic, and renal circulation (Fig. 31.5) when an intra-aortic balloon pump (IABP) was in place. If the left ventricle is not sufficiently drained and signs of pulmonary circulation overload are evident despite all these

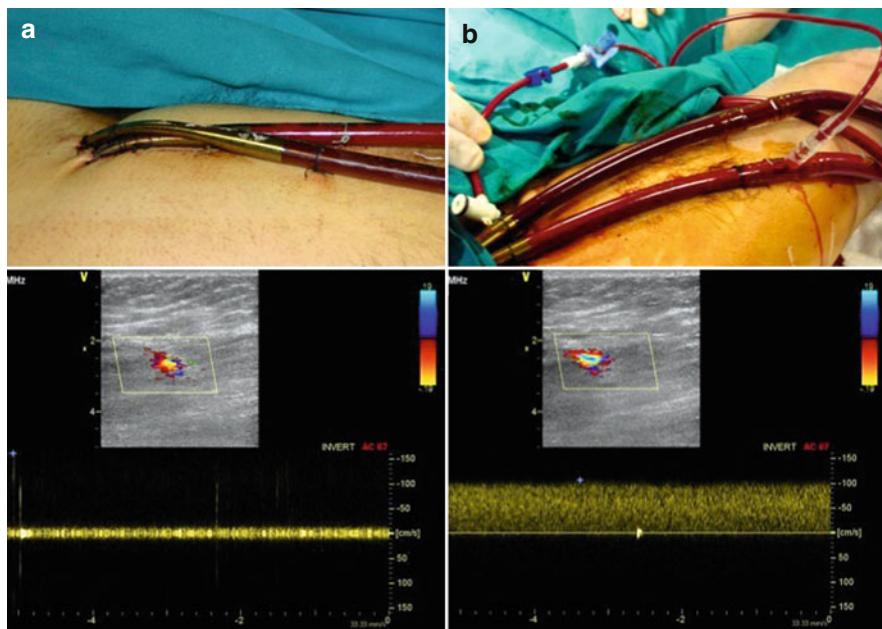


Fig. 31.6 Flow variation in anterior tibial artery before (a) and after (b) positioning of a distal reperfusion cannula in common femoral artery

measures, an active drainage of the left ventricle is mandatory. Various techniques have been described in literature [5, 6], but the most common technique in adult patients is represented by apical venting of the left ventricle; in this case, echocardiography can be used to verify the correct placement and function of the venting cannula. We also recently described an alternative technique of transpulmonary drainage, in which the echocardiographic control is important during positioning of the drainage cannula and, still, to verify the efficacy of venting [7].

Echocardiography, through the evaluation of transaortic flow, represents a valuable tool to measure cardiac output during ECMO support: The thermodilution techniques in fact appear largely unreliable because of the variable blood “steal” caused by the venous drainage cannula, and the methods based on “pulse contour” cannot always be used because of the scarce pulsatility in the peripheral arteries when the ECMO flow is high.

During all the course of support, it is important to constantly monitor the perfusion of the cannulated limbs, to detect early when a peripheral reperfusion is needed, and to control its effectiveness (Fig. 31.6).

31.5.3 Intermediate Stage (Detecting Complications)

Patients supported on ECMO are critically unwell and thus at increased risk for complications due to the underlying disease process, critical illness, anticoagulation, or the device itself, particularly after cardiac surgery. Echocardiography can

assist in the detection and management of specific complications that may arise during ECMO support. It is usually the first investigation requested when there is a suspicion of ECMO malfunction, particularly for thrombosis, cannula displacement, or pericardial tamponade. A significant number of transthoracic and transesophageal echocardiographic studies are performed on patients who are on ECMO [8, 9]. Because of the limitations of spatial resolution with TTE, TEE is usually required to detect these complications. It enables rapid assessment of cannula positioning, cardiac filling and function, chamber compression from tamponade, and cannula-associated thrombi.

The detection of cardiac tamponade and the significance of pericardial effusions or collections can be difficult in patients supported on ECMO, as the heart is in a partially bypassed state. There may be significant compression of a cardiac chamber from a pericardial hematoma, but if this does not adversely affect cannula flow, it may be of no hemodynamic significance.

The presence of a significant pericardial collection, which may even result in cardiac chamber compression and may not necessarily affect hemodynamics or ECMO flow while on support, may become a significant factor when contemplating weaning from ECMO.

The cannulas used in ECMO can be large, which predisposes them to being a common cause of complications, especially thrombosis or venous and arterial obstruction. Thrombus formation associated with venous cannulas may either reduce ECMO flow or complicate the clinical course by causing a pulmonary embolism. Additionally, on removal of a venous ECMO cannula, organized thrombi that had formed around the cannula may be left behind in the heart. If the venous cannulas are removed at the time of surgery (such as during VAD insertion or cardiac transplantation), it is recommended that intraoperative TEE of the inferior vena cava be performed to assess for the presence of a venous cannula cast. If missed, this may subsequently cause pulmonary embolization.

31.5.4 Final Stage (Recovery and Weaning)

The final area in which echocardiography plays an important role is the determination of recovery and readiness for weaning from ECMO support. For VA ECMO, this may be performed under direct echocardiographic visualization and guidance with or without a pulmonary artery catheter. The decision to wean ECMO support and its timing are complex. Cardiac recovery is often marked by increasing pulsatility seen on the patient's arterial line tracing. For VA ECMO, it would be unusual to attempt to wean ECMO in the first 72 h [10]. As a general rule, it is possible to evaluate the possibility of weaning a patient from ECMO support when the problems that led to the assistance (ischemic, arrhythmic, septic, etc.) are under control and the hemodynamic status is stable.

The level of recovery and the likelihood for weaning ECMO support are based on a multitude of clinical, hemodynamic, and echocardiographic variables which are extensively addressed in a specific chapter. Echocardiographic parameters that may suggest an attempt to cease ECMO support include an adequate LV ejection

fraction, an LV outflow tract velocity-time integral >10 cm, and the absence of LV dilation and of signs of cardiac tamponade [11, 12]. Few data have been published outlining methods and findings during ECMO weaning. In a study by Konishi et al. [13], Doppler evaluation of flow in the descending aorta was used to help determine cardiac recovery after viral myocarditis treated with peripheral VA ECMO. The authors commented that the level at which the two flows mix may be of benefit in determining whether adequate cardiac output is being generated by the native heart. In another study [14], to evaluate hemodynamic and functional changes of the failing left ventricle by velocity vector imaging (VVI) and tissue Doppler, 22 patients with cardiogenic shock supported by extracorporeal life support (ECLS) were imaged during ECMO output variations inducing severe load manipulations. Load variations were documented by a significant decrease in afterload (mean arterial pressure), an increase in preload (left ventricular end-diastolic volume, E, E/Ea ratio all increased), and an increase in the velocity-time integral. VVI parameters increased, unlike tissue Doppler systolic velocities. The authors concluded that VVI parameters are load dependent, like conventional Doppler echocardiographic data, while the systolic velocities of the mitral annulus measured by Doppler tissue imaging (Sa) were found to be load independent and to have significant prognostic value for predicting ECMO weaning. Sa was higher (>6 cm/s) in patients who survived.

When weaning VA ECMO, a common approach is to reduce the ECMO flow in 0.5–1.0 L/min increments and assess the clinical and hemodynamic parameters (including heart rate, blood pressure, arterial waveform pulsatility, oxygen tension level in a right radial arterial line, and changes in central venous pressure and pulmonary artery pressure) and echocardiographic parameters (stroke volume, ventricular dimensions, ventricular volumes, and ejection fraction) [15]. ECMO flows are usually not reduced below 1–2 L/min, because of the increased risk for circuit thrombosis at low-flow rates. If the patient remains hemodynamically stable at flows as low as 1 L/min, we can suppose that the patient is ready to be disconnected from support. The ECMO flow is raised up to the pre-test level so that anticoagulant drugs can be stopped to facilitate the hemostasis during the phase of decannulation. A slow and progressive weaning from support enables to accurately predict when a patient is ready to be disconnected; however, because the pump cannot be completely stopped during the assistance for thromboembolic reasons, decannulation represents a delicate phase, and a careful hemodynamic and echocardiographic evaluation is needed to promptly identify and treat contingent problems.

After decannulation and hemostasis of the vascular access sites, ultrasounds are extremely useful to verify possible damage to the cannulated vessels and to tissues around them (laceration, pseudoaneurysms, relevant hematomas).

31.6 Venovenous ECMO

In patients with severe respiratory failure who need an extracorporeal assistance, it is important to provide the appropriate support. Venovenous ECMO (VV ECMO) usually represents the best option: It has fewer vascular complications, keeps the lung perfusion intact allowing a better pulmonary penetration of antibiotics, and

provides a better oxygen delivery to the upper part of the body (especially brain and heart) which may be impaired during a VA ECMO.

During a venovenous assistance, it is of paramount importance to ensure an adequate cardiac function, sufficient to completely sustain the circulation. Therefore, before establishing a VV support, a complete evaluation of both echocardiographic and hemodynamic parameters of the patient is essential. As for VA ECMO, the exam has to be complete, paying particular attention on the estimation of pulmonary pressure derived from tricuspidal regurgitation, and on the function and dimensions of the right ventricle, which is one of the major determinants, with sepsis, of cardiac insufficiency in patients with ARDS.

The venovenous assistance has generally no significant impact on cardiac performance. In fact as blood is taken from and then returned to the right heart, there is no significant change in RV preload, and there is no adverse effect in hemodynamics in the normal left heart. During VV ECMO, the pulmonary circulation receives blood with increased oxygen content and increases the mixed venous oxygen saturation. This may have two beneficial effects. First, it may decrease pulmonary vascular resistance, leading to lower RV afterload. Second, it may indirectly improve LV function by increasing oxygen delivery to the left heart and hence coronary arterial circulation. Sepsis and increased pulmonary vascular resistance in response to significant hypoxemia may adversely affect RV function. Echocardiography can be useful in documenting the effects of improving oxygenation and acid–base status on the adequacy of RV function when VV ECMO is applied.

As for VA ECMO echocardiography is useful to guide the correct placement of the cannulae. Venous cannulae may be placed through a femoral or internal jugular approach. As a general rule, the tip of the return cannula should be placed in the mid right atrium, clear from the interatrial septum and tricuspid valve, i.e., more proximally than the tip of the drainage cannula. If the access cannula is placed more proximally than the return cannula, or if the two cannulae ends are too close, recirculation will occur, resulting in a reduction in the efficiency of the system and in the amount of oxygenated blood passing into the pulmonary and systemic circulation. Echocardiographic assistance can also help in detecting abnormal positioning of a cannula against the interatrial septum, through a patent foramen ovale and into the left atrium, in the coronary sinus, and across the tricuspid valve or subvalvular apparatus. Cannula malpositioning may also result in vascular or cardiac injury and inadequate flows.

Imaging is recommended for placement of the Avalon Elite cannula [16]. These dual-lumen cannulas are inserted via the right internal jugular vein. One lumen has specifically located holes that drain blood from the inferior vena cava and superior vena cava. The other lumen returns blood to the right atrium through a side hole that is positioned to face the tricuspid valve. Meticulous positioning is required so that the cannula tip is located in the inferior vena cava just below the cavo-atrial junction and the return side hole is positioned to enable return flow across the tricuspid valve [17].

Even though VV ECMO is the assistance of choice for patients with respiratory failure, in some cases the cardiocirculatory status is inadequate to sustain the patient's hemodynamics. Also, in septic patients or in patients with severe

pulmonary hypertension, an acute cardiac insufficiency can develop during the period of support. For this reason, even in patients needing mostly respiratory support, an “echo-dynamic” approach (based on the combination of echographic and hemodynamic data) is advisable to identify and treat early a potential worsening in cardiac function and to predict the need for a change to a circulatory assistance (venoarterial or veno-artero-venous ECMO).

31.7 Conclusions

Ultrasounds play a fundamental role in managing patients supported with ECMO during all the different stages of assistance, from indication to cannulation, monitoring, and weaning. Either during circulatory or respiratory assistance, ultrasounds are fundamental to evaluate the cardiac function of the patients, providing information that determines appropriate patient selection. They are also needed to choose the best vascular access sites, guide the insertion of cannulas, monitor progress, detect complications, and help in determining recovery and weaning of support.

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32.1 Introduction

Critically ill patients submitted to ECMO (extracorporeal membrane oxygenation) routinely require an advanced haemodynamic monitoring to evaluate either the cardiovascular function or the effectiveness of the cardiopulmonary bypass. Adequate monitoring should be focused on the evaluation of the underlying life-threatening cardiac and/or respiratory disease in order to assess both the severity of the cardiac and/or respiratory failure and the eventual recovery from organ failure. Proper haemodynamic monitoring can also help decide the timing of weaning from the mechanical circulatory support.

Veno-arterial (VA ECMO) is generally employed for the treatment of refractory cardiogenic shock due to different causes (post-cardiotomy, post-heart transplant, cardiomyopathy, myocarditis, acute coronary syndrome). Veno-venous (VV ECMO) is used for the treatment of severe respiratory failure primarily due to adult respiratory distress syndrome (ARDS), pneumonia, trauma or primary graft failure following lung transplantation [1, 2]. Despite VA and VV ECMO being generally employed in different pathological populations, cardiac failure can be present in patients with severe respiratory failure requiring extracorporeal mechanical device [3].

32.2 Haemodynamic Monitoring

The goal of the haemodynamic monitoring in the ECMO patients is to provide information about the adequacy of the organs and the peripheral perfusion [4].

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32.2.1 VA ECMO

Patients with severe cardiac dysfunction, submitted to the VA extracorporeal mechanical support, can easily suffer from low cardiac output (CO) syndrome because of either the underlying cardiogenic shock or the presence of the cardiopulmonary bypass (CPB). Adequate haemodynamic monitoring should provide information about either the underlying cardiac disease evaluating the patient's cardiac performance or the effectiveness of the ECMO support [5].

ECMO should adequately support the patient's baseline cardiac performance in order to achieve an optimal tissue perfusion, providing adequate flow rates and oxygen supply.

In this contest, the main target of the haemodynamic monitoring is the evaluation of the global tissue perfusion. In addition, a good cardiopulmonary monitoring should correctly define the haemodynamic profile of the patient in order to guide the therapy and follow up the progression of the underlying disease. The optimization of either the oxygen delivery or the haemodynamic status can result from the information acquired by the correct haemodynamic analysis. For all these considerations, the most appropriate haemodynamic monitoring for the patients in VA ECMO should be focused on the evaluation of the patient's cardiac function (throughout the echocardiographic assessment of the heart function at the various steps of the mechanical support and the measure of both the CO and the mixed venous oxygen saturation (SvO_2)) and on the efficiency of the mechanical device to sustain the cardiocirculatory function and the organ perfusion (throughout the monitoring of the SvO_2 , the urinary output and the blood lactate values).

32.2.1.1 Cardiac Output

Although echocardiography remains the best tool to evaluate the cardiac function, many monitoring systems that provide the continuous assessment of the CO are actually available. Among them the pulmonary artery catheterization (PAC) with the Swan-Ganz catheter is still considered the gold standard of haemodynamic monitoring [6]. Although the role of the PAC is still the object of discussion among the scientific community, nevertheless its limitations and contraindications, the pulmonary artery catheterization provides many information about the haemodynamic profile of the critically ill patient [7, 8]. Pulmonary artery pressures and left and right cardiac chamber pressures can be directly measured by pulmonary artery catheterization, and both CO and mixed venous oxygen saturation (SvO_2) can be continuously displayed by the most recent monitoring instrumentations. In addition, PAC allows the calculation of other derive haemodynamic parameters including the systemic and pulmonary vascular resistances [4].

Because PAC is an invasive technique and the haemodynamic data collected by the pulmonary artery catheterization can be misinterpreted in some clinical contests (e.g. tricuspid regurgitation), several either minimally invasive or absolutely noninvasive CO monitoring systems have been recently introduced in the clinical scenario. The most common techniques employed for the measure of the CO are listed in Table 32.1.

Table 32.1 Minimally invasive technique for CO monitoring

Fick principle
Pulsed Doppler technology
Echocardiography
Pulse contour analysis
Bioimpedance
Bioreactance

32.2.1.2 SvO_2

The maintenance of the adequate tissue oxygen supply–demand balance is fundamental in the critically ill patients on ECMO. The conduct of the extracorporeal mechanical device should provide an optimal tissue perfusion throughout the management of the different pathophysiological variables encountered during the ECMO assistance.

The SvO_2 , measured in the main pulmonary artery with the Swan-Ganz catheter, has been largely recognized as a good indicator of the global tissue perfusion provided by both the patient's cardiac performance and the extracorporeal assistance. According to the Fick principle, SvO_2 value results from the combination of five major variables (Fig. 32.1):

$$\text{SvO}_2 = \text{SaO}_2 - (\text{VO}_2 / \text{CI} \times \text{Hb} \times \text{PO})$$

where SaO_2 arterial, O_2 saturation, CI cardiac index, PO O_2 affinity, Hb oxyhaemoglobin content.

SvO_2 does not always correspond to the effective tissue O_2 tension (PvO_2) that depends on the position on the oxyhaemoglobin dissociation curve. During ECMO the continuous variation of either the haemodynamic parameters or the haemoglobin content and the arterial blood oxygenation makes the trend of the SvO_2 values a better indicator than an absolute value of mixed venous oxygen saturation of the matching between the oxygen delivery (DO_2) and the oxygen consumption (VO_2) [9]. As it is clearly showed by the Fick equation, the variation of any of the determinants of the SvO_2 can lead to significant changes of the SvO_2 values during its continuous monitoring. Because the relationships among the five components of the equation are mathematically different and it is uncommon that only one of the variables changes independently from the others in a clinical contest, a “normal” value of SvO_2 is quite difficult to define; it has been demonstrated that a SvO_2 range between 60 and 80 % suggests an appropriate peripheral perfusion.

Although the measurement of the SvO_2 during ECMO generally correctly reflects the effectiveness of the tissue perfusion, sometimes SvO_2 value could not adequately indicate the global perfusion.

Although the SvO_2 expresses the match between DO_2 and VO_2 , the value of the SvO_2 calculated in the main pulmonary artery could not reflect the eventual regional distribution of the blood flow and the different perfusion of the different body districts. It should be considered that during VA ECMO, low coronary and/or cerebral flow can occur because of a certain degree of deoxygenated and oxygenated blood mixture at level of the descending thoracic aorta.

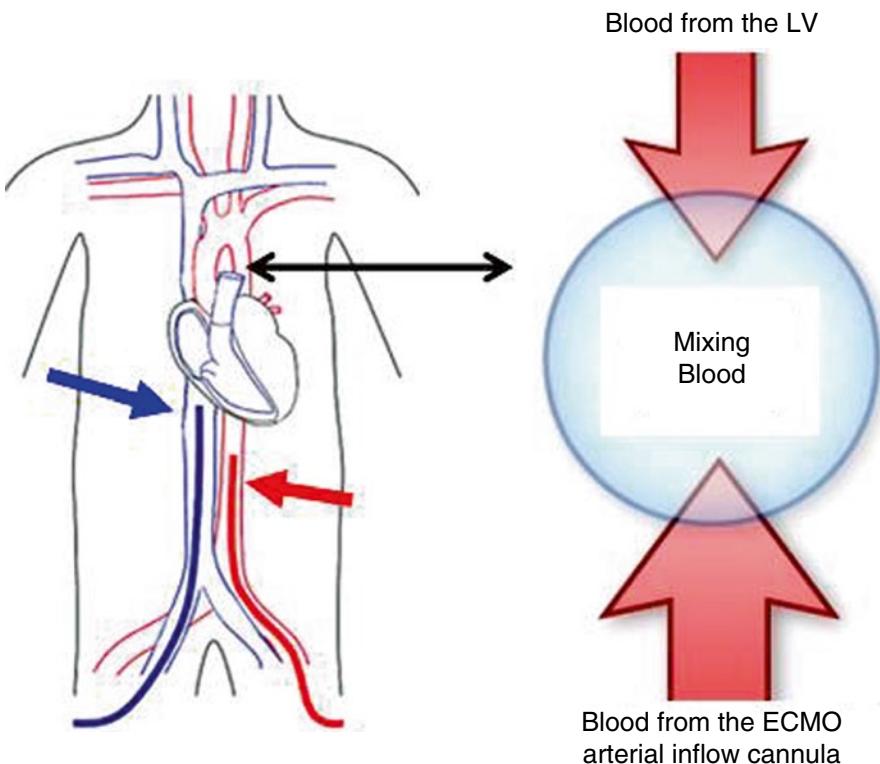


Fig. 32.1 VA ECMO with femoral approach. Left panel: the arrows indicate the venous (blue arrow) and arterial (red arrow) cannulas. Right panel: the black double arrow indicates the proximal part of the descending aorta where the blood mixture of the oxygenated blood coming from the arterial cannula and the less oxygenated blood running from the patient's LV can occur. The location of the arterial cannula inside the descending thoracic aorta leads to a mixture between the oxygenated blood coming from the ECMO circuits and the less oxygenated blood ejected by the LV

32.2.2 VV ECMO

Patients submitted to VV ECMO do not generally present cardiac function impairment, since severe respiratory dysfunction requiring extracorporeal support because of being a nonresponder to the conventional therapy can occur in patients with chronic pulmonary hypertension and right heart decompensation. Therefore, cardiac dysfunction can coexist with respiratory failure even when a cardiocirculatory support is not required. Because VV ECMO do not provide circulatory support, it has generally few effects on the systemic haemodynamic. This is not always true because it should be considered that the high blood flow in the pulmonary artery would increase the pulmonary vascular resistances (PVR) with consequent increase of the right ventricle (RV) afterload that can lead to RV failure. For this reason the patients in VV ECMO require an advanced haemodynamic monitoring too.

VV ECMO supports the respiratory function providing an adequate arterial oxygenation and CO₂ removal. The adequate monitoring during VV ECMO should be

focused on the effectiveness of the respiratory support provided by both the extracorporeal help and the patient's breathing [10]. The arterial oxygen saturation and the SvO_2 are the best indicators of the respiratory profile. According to the guidelines, the respiratory support provided by the VV ECMO is considered adequate when the $\text{SaO}_2 > 80\%$ and $\text{SvO}_2 > 70\%$ [11]. As reported by some recent literature, low tissue oxygenation and low perfusion are associated with worse outcome. For this reason higher values of SaO_2 could be required in patients under VV ECMO to maintain an adequate organ perfusion [5]. In VV ECMO the arterial oxygenation strictly depends on the blood flow, so the higher is the flow through the circuit, the better is the oxygenation. Conversely, because the CO_2 is highly diffusive, low blood flows are generally sufficient to provide decarboxylation. Blood gases can be easily measured by blood samples obtained from the patient's arterial line.

Hypoxaemia, and consequently low SvO_2 , can frequently occur in VV ECMO because of different mechanisms. One of them is the recirculation. Recirculation is an unavoidable effect of the VV ECMO depending on the aspiration back into the extracorporeal circuit of a variable portion of the oxygenated blood previously infused in the right atrium (RA) [12]. This phenomena is strictly correlated to the physical characteristic of the venous cannula and to the position of the proximal and distal lumen on the same cannula [13, 14]. The main effect of the recirculation is that the blood in the RA can be poorly oxygenated and the oxygen delivery can be decreased, leading to global and/or regional hypoperfusion. For the presence of the recirculation, the value of the mixed venous saturation measured at the venous line of the ECMO circuit is not always appropriate. SvO_2 should be directly measured in the pulmonary artery by the Swan-Ganz catheter which can be considered a better indicator of the global perfusion. Another significant cause of hypoxaemia during VV ECMO is the mixture between the oxygenated blood coming from the circulatory support and the low oxygenated blood running from the patient's vena cavae. In the RA the blood oxygen content decreases, and the tissue oxygenation is lower than that required.

32.2.2.1 Harlequin Syndrome

Patients submitted to percutaneous VA ECMO can suffer from regional low perfusion despite adequate oxygenation and pump flows rate being preserved [2]. The proximal cannula is generally located in the upper part of the descending thoracic aorta. Because ECMO provides up to 80 % of the global blood flow and a native flow through the patient's aortic valve is preserved, a mixture of the oxygenated blood coming from the arterial cannula and the less oxygenated blood running from the patient's left ventricle (LV) can occur (Fig. 32.2). Therefore, the O_2 content of the blood in the ascending aorta can decrease. Because of the anatomic position of the coronary arteries and of the epiaortic vessels, the myocardial and the cerebral flow are at main risk to receive low oxygenated blood [15]. The coronary arteries' hypoperfusion can result in myocardial ischaemia with consequent worsening of the heart function, limiting the organ recovery. The cerebral hypoperfusion can lead to moderate to severe neurologic complications that can negatively impact on the patient's outcome [16].

The alteration of the regional perfusion can lead to severe organ dysfunction; the absolute value of the SvO_2 as well as its variations in the range of normality measures



Fig. 32.2 The figure shows a case of ECMO in which a multimodal monitoring was applied: note the transesophageal echo probe in site and the NIRS monitoring displaying the cerebral saturation

Table 32.2 Information on ECMO flow obtained by coupling NIRS and SvO_2 monitoring

NIRS	SvO_2	Flow
Normal	Normal	Adequate
Reduced	Reduced	Reduced
Reduced	Normal	Normal but not adequate

cannot represent the mismatch between the DO_2 and VO_2 occurring in some of the body districts (mainly in the coronary and cerebral flow) (Table 32.2). For this reason a multimodal monitoring approach should be considered. The coronary flow may be investigated with echocardiography, and the cerebral flow should be assessed with neuromonitoring systems like the near-infrared spectroscopy (NIRS) (Fig. 32.2).

The double check between the global SvO_2 and the regional SrO_2 provided by the NIRS monitoring can lead to a better interpretation of the haemodynamic assessment, revealing any significant variation of the tissue perfusion [17].

32.3 Conclusions

1. The haemodynamic monitoring in the ECMO patients should basically investigate the effectiveness of the cardiocirculatory and/or respiratory support.

2. Any information about the global tissue perfusion in VA ECMO and about the gas exchanges in VV ECMO should be promptly acquired by the appropriate tools.
3. The most adequate monitoring system should be chosen according either to the underlying disease or to the type of mechanical support provided.
4. The haemodynamic monitoring should provide information about the progression of the disease and the eventual recovery from organ failure.
5. The haemodynamic monitoring should guide the therapy evaluating the response of the patient to the treatment.
6. The appropriate haemodynamic monitoring should allow the optimization of the clinical and mechanical support.

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Respiratory Monitoring During VA ECMO

33

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Venoarterial extracorporeal membrane oxygenation (VA ECMO) represents an excellent support in severe cardiogenic shock. Arterial oxygenation is largely provided by the oxygenator, while the flow through the pulmonary circulation is dramatically reduced, because blood is drained from the right atrium by the venous cannula to the circuit and returns to the patient through the arterial line [1, 2]. Therefore, it is difficult to evaluate the lung function during ECMO support, even though the lung might not be initially affected.

Why do we need to know lung function during VA ECMO? The main reason is to allow VA ECMO weaning when heart function has recovered.

33.1 How Can Lung Function Deteriorate During VA ECMO?

One of the main causes is left ventricular congestion. During VA ECMO, if the left ventricular function is completely depressed, the blood coming from the bronchial arteries to the left atrium cannot be ejected easily, resulting in a left ventricular distension with deleterious effects on heart and lung. In turn, left ventricular congestion increases the venous pulmonary pressure and induces pulmonary oedema. Although this might be clinically irrelevant during VA ECMO because the oxygenator provides gas exchange, it becomes pivotal when the cardiac function recovers

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and the VA ECMO might be removed. Hence, a persistently congested lung might be compromised in its function and drive to a severe respiratory failure, which blocks weaning from the extracorporeal device [3]. An experimental study showed the histological damage of the lung after prolonged VA ECMO: morphological changes of the lungs varied from frank pulmonary oedema to alveolar haemorrhage and pulmonary parenchymal necrosis. This histological phenomenon could explain the reduction of compliance after weaning from the VA ECMO [4]. A recent observational study, performed on patients undergoing VA ECMO for refractory cardiogenic shock, who required long-term mechanical circulatory support (MCS), showed that 27 % developed acute lung injury during extracorporeal support, increasing the rate of weaning failure for hypoxaemia and the rate of early mortality (87 %). This complication might be explained by different mechanisms, such as a pre-existing unrecognized lung injury at VA ECMO implantation, or it might be related to persistency of pulmonary oedema, or it might be due to a systemic inflammatory response syndrome and multi-organ dysfunction [5]. Furthermore, Chen et al. observed during the first 96 h after VA ECMO implantation that one of the main factors predicting weaning failure and a poor outcome might be lung dysfunction [6]. Ensuring early an adequate left ventricular unload might prevent or reduce this phenomenon.

33.2 How Do We Monitor the Lung Function?

The chest X-ray might be useful to evaluate the level of oedema, but it does not give us a clear idea of the real lung function and it could be misleading. Haemodynamic monitoring with the pulmonary catheter might be useful to evaluate and follow the unloading of the left atrial and ventricular pressure, which might represent an indirect measurement of pulmonary congestion. Furthermore, the haemodynamic monitoring with PiCCO has been used during veno-venous ECMO, and it might be useful to calculate the extravascular lung water index (ELWI) and giving an estimation of the degree of the pulmonary oedema [7]. During VA ECMO this kind of monitoring is useless because the pump function of the heart is largely supported by the extracorporeal device; therefore, cardiac output through the lung is markedly reduced, and it does not allow the measurement of ELWI. A more recent and interesting alternative method to monitor lung parenchyma might be chest ultrasound examination. This method is easy to perform at bedside, and it is inexpensive and in certain case might be more sensitive than chest X-ray: in fact interstitial oedema can be diagnosed with 97 % of sensitivity and 95 % of specificity, when three or more “B lines,” which are typical hyperechoic artifacts (ring-down artifacts), are present. Furthermore, it is highly sensitive for the evaluation of pleural effusion and parenchymal consolidation, even superior to chest X-ray, and some authors proposed to use ultrasound to differentiate acute respiratory distress syndrome from pulmonary oedema [8–10].

33.3 Lung Management

Mechanical ventilation during VA ECMO should be as protective as possible to avoid ventilatory-induced lung injury, although lung injury is not usually present when mechanical circulation support (MCS) is positioned. Since the lung does not contribute to a relevant extent to gas exchange when VA ECMO provides total assistance, tidal volume and minute ventilation should be reduced and positive end-expiratory pressure (PEEP) should be optimized to keep the lung open and to reduce atelectasis. Several authors showed that injurious mechanical ventilation with high tidal volumes and high peak inspiratory pressures might be associated with an increased risk of developing acute lung injury in ventilated patients without lung injury [11, 12]. Usually, to ensure lung protection, some authors suggest to maintain a peak inspiratory pressure lower than 20–25 cmH₂O, PEEP at 10–15 cmH₂O, and respiratory rate lower than 10 per minute with a FiO₂=30 % [13]. During extracorporeal support, respiratory mechanics should be routinely monitored, because compliance might be modified by the increase in oedema or the development of acute lung injury, due to inflammatory processes or flogistic infiltrations [4, 14]. However, respiratory mechanics do not give us a real estimation of the lung function in term of gas exchange: in fact in some cases, compliance could be normal, but the oxygenation capability could be extremely low, because of acute pulmonary oedema. Therefore, during VA ECMO, it is extremely important to ventilate the lung gently and to avoid atelectasis, while the unloading of the left ventricle should be the priority to reduce the risk of pulmonary congestion and oedema.

How can the left ventricle be unloaded? Different methods have been proposed:

1. The most common technique in adult patients is represented by the use of intra-aortic balloon counterpulsation with the aim of reducing afterload and increasing coronary perfusion [5].
2. Another possibility is the decompression of the left atrium with a transseptal cannula incorporated in the circuit, which allows the unloading of the pulmonary venous circulation and might reduce the pulmonary congestion [3].
3. An alternative percutaneous method might be performed by a pulmonary arterial catheter, which drains the residual blood in the pulmonary circulation and the left atrium to the venous line of the ECMO circuit [15].
4. A further option, by using the percutaneous approach, is the Impella microaxial flow pump, which permits the direct drainage of the left ventricle [16].

Recently a new method to unload the left ventricle was implemented. The novel approach is performed by a mini-thoracotomy with a Seldinger technique using an arterial high-flow cannula, inserted in the apex of the left ventricle (transapical left ventricle vent, TLVV). This system allowed the drainage of blood and might reduce the wall tension of the ventricle and the pulmonary congestion. TLVV is connected to the venous inflow line and contributed to total flow, before the oxygenator. This new system might allow switching from a VA ECMO to a short-term left

ventricular assist device (L-VAD), if the right ventricular function is maintained and the lung function is good. The great advantage on the standard L-VAD is that an oxygenator is available in the circuit and gives the possibility to evaluate the pulmonary function gradually [17]. In our centre, from January 2010 to June 2012, 16 patients supported by peripheral VA ECMO for cardiogenic shock underwent TLVV implantation. All patients were switched to a short-term L-VAD in two phases: first, patients were weaned from the right ventricle support (arterio-arterial ECMO), and then they were weaned from the oxygenator. During this second phase, blood gases were analyzed before the oxygenator and from the arterial line of the patient, with the same FiO_2 both at the oxygenator and at the mechanical ventilator, to obtain a baseline value. Then, the FiO_2 of the gas blender of the oxygenator was set at 21 % and other two samples were obtained, to decide if the oxygenator could be removed [18]. Additionally, continuous monitoring of end-tidal CO_2 provides a fundamental guide to tailor ventilation in order to ensure an adequate PCO_2 and pH in the lungs. It becomes often necessary to add dead space on the ventilator circuit to optimize local pH when this remains too high despite a reduction in minute ventilation.

Furthermore, during VA ECMO, patients can also breathe spontaneously in the absence of primary respiratory failure. However, ECMO could be a specific challenge for the respiratory control system because it reduces the venous return to the pulmonary circulation dramatically and with variable proportion, while aortic blood flow, mean arterial pressure, and CO_2 remain unchanged. A group of authors reported a case where the increased of PaCO_2 induced by the reduction of the gas flow to the oxygenator did not change the breathing pattern of the patient, while an increase of the venous return to the right atrium and ventricle obtained with the reduction of the blood flow on the ECMO circuit did, with an increase in the respiratory rate [19]. This mechanism has been described only in an experimental model of VA ECMO, where the acute rise in pressure in the pulmonary artery and right ventricle or in the left atrium might modify the breathing pattern, independently from neural control [20, 21]. Further clinical studies are needed to better understand the mechanism of control of breathing during VA ECMO.

33.4 Conclusions

In conclusion during VA ECMO, a proper respiratory monitoring is difficult to perform, but the keys to preserve the lung function are the unloading of the left atrium and ventricle and a protective lung ventilation strategy. Further studies are needed to evaluate the neural control of breathing during VA ECMO, when the blood diverges from the right atrium and ventricle and the pulmonary circulation to the ECMO circuit.

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34.1 Introduction

Neurological monitoring during extracorporeal membrane oxygenation (ECMO) is one of the most challenging tasks in an intensive care unit because of the complexity of the clinical scenario and the instability of the patient, who is most often in a comatose condition just before the onset of extracorporeal circulation.

In this context, neuromonitoring is an extension of clinical examination that is often unfeasible because of multi-organ failure, sedation, and hypothermic

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treatment. In particular, after the advent of therapeutic hypothermia, clinical evaluation has been called into question because of its higher rate of producing false positives. A multimodal neurophysiological strategy can overcome this limitation and provide additional information on brain function, blood-flow velocity, and brain oxygenation. This strategy allows targeting of not only the level of neuroprotection but also the haemodynamic and respiratory parameters to be maintained during the extracorporeal treatment.

Neurological monitoring can be extemporaneous or continuous based on available miniaturised technologies and the severity of the patient's condition. Moreover, it plays a critical role in the diagnosis and prognosis of the neurological dysfunction.

34.2 The Value of a Multimodal Strategy

Because the pathogenesis of brain damage during ECMO can be multifactorial, monitoring instruments should be used to obtain information on the status of brain function, like EEG and somatosensory evoked potential. Circulatory pathogenetic mechanisms that predispose the patient to functional damage should also be checked, such as embolisation and hypoperfusion, through methods, such as transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), or jugular oxygen saturation (SjO_2), and biochemical markers of brain injury [1–3] (Fig. 34.1).

34.3 Neurophysiological Monitoring of Brain Function

Brain function can be monitored directly by EEG and SEPs, the spectrograms of which correlate directly with CBF (cerebral blood flow) [4, 5]. A gradual reduction in cerebral perfusion is associated initially with changes in synaptic transmission and at the end with neuron death due to the impossibility of maintaining the electrochemical gradient of the cell membrane. Normally, CBF is approximately 50–80 ml/100 g/min. Moderate hypoperfusion up to values of 30 ml/100 g/min is well tolerated and does not cause neuron dysfunction; when the flow decreases below the functional limit (25 ml/100 g/min), both the EEG and SEPs begin to change. The functional limit is not time dependent, but the injury limit is. The necrosis area increases with time beyond the injury limit.

EEG and SEPs disappear at flow values of about 12–15 ml/100 g/min, although some authors consider that cortical SEPs disappear at a flow that is 20 % less than the flow necessary to bring about an isoelectric EEG [6].



Fig. 34.1 Continuous multimodal neuromonitoring during postcardiotomy ECMO; on the *upper side*, the neurophysiological, NIRS, and TCD monitoring are highlighted

Between the functional and injury limit is the ischaemic penumbra: the brain tissue in this area is electrically silent and not functional but still vital [7]. The ischaemic penumbra is a dynamic area extending from the periphery of an infarcted area, and its progression from functional damage to structural damage depends on the timing and efficacy of therapy.

The ischaemic penumbra can evolve to functional recovery if the flow increases or to necrosis if the ischaemia persists. Thus, the potential regression of the ischaemic penumbra area introduces a basic concept for brain recovery that is directed at preventing or minimising a secondary lesion by improving DO_2 , reducing CMRO_2 (brain metabolism), and reducing reperfusion damage. There is no doubt that the duration and size of the ischaemia influence the degree of brain damage. There are regional differences in resistance to ischaemic damage that depend on metabolic activity, differing susceptibility to ischaemia, availability of collateral pathways, and capillary density. A reduction in EEG and SEP amplitude, slowing of the EEG, and increased latency of the SEPs indicate that the functional limit of CBF has been reached.

These changes are extremely important during extracorporeal perfusion of the patient because they provide an alarm signal that goes off before the brain lesion becomes irreversible. If the proper steps are taken to increase the CBF (increasing the pump rate or administering vasoconstrictors) or in general the DO₂ and reduce brain metabolism (increasing the depth of sedation or level of hypothermia), the functional limit will not be reached.

34.3.1 EEG

Much of the literature agrees that gradual reduction in CBF produces an attenuation in the EEG with amplitude reduction and slowing at a frequency expressed by a reduction in alpha rhythm (α , 8–13 Hz) and beta rhythm (β , >14 Hz) and an increase in theta rhythm (θ , 5–7 Hz) and delta rhythm (δ , 0.5–4 Hz). These changes can be generalised (global ischaemia) or regional (focal ischaemia). The degree of ischaemia is associated with the severity of the electroencephalographic changes; the EEG cannot evaluate the entire cerebral cortex and is less effective in distinguishing changes in subcortical structures. In addition, the asymmetry between the hemispheres is considered significant in patients given stable sedation or anaesthesia to induce electroencephalographic suppression.

The EEG changes may have latency from 10 s after a cardiac arrest [8] and up to 3 min after an embolic injury [9]. In general, the EEG has had a secondary role with respect to the somatosensory evoked potentials in given information about the neurological prognosis; recently, some studies have pointed out the high predictive value of an accurate neurological prognosis from a good and reactive EEG in the acute phase of post-anoxic coma. A good EEG is considered a continuous pattern without a period of suppression, while isoelectric or low voltage and burst suppression are considered EEG patterns associated with a negative outcome [10]. Moreover, one of the most important EEG patterns that can be detected is nonconvulsive status epilepticus; rapid recognition guarantees early treatment.

Fourier spectral analysis is an established method of quantitative analysis of the EEG and is useful for providing data in tighter groups for easier interpretation and early identification of brain ischaemia [11]. The data from the Fourier analysis can be presented in the form of CSA (compressed spectral analysis) or DSA (modulated-density spectral analysis); CSA and DSA are both graphic representations based on finding a total reduction in the power of the tracing and/or an increase in the power of the components in the θ - and δ -slow bands (Figs. 34.2 and 34.3).

34.3.2 Somatosensory Evoked Potentials (SEPs)

SEPs are used more than BAEPs (brainstem auditory evoked potentials) and VEPs (visual evoked potentials) to find cerebral ischaemia because they provide a direct correlation between function and perfusion of the territory of the middle cerebral artery. They are less sensitive to pharmacological depression brought about by the anaesthetic agents and are also easier to monitor because the cortical somatosensory projections are located on the convexity of the hemispheres.



Fig. 34.2 TCD-EEG coupling during ECMO. *Left side:* a nonconvulsive status epilepticus at EEG (*lower*) induced an increase of blood-flow velocity at TCD (*upper*). *Right side:* showers of gas microemboli (*TCD upper*) induced a further decrease in amplitude of EEG signals (*lower*)

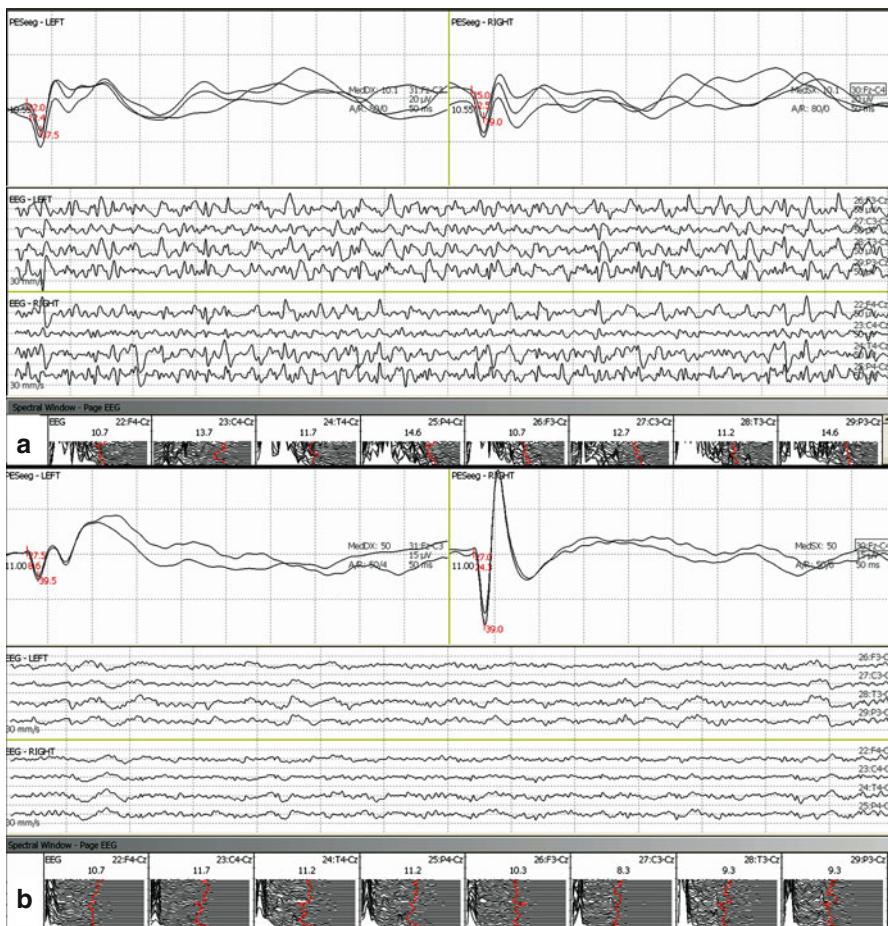


Fig. 34.3 Two possible neurophysiological scenarios of patients with good outcomes. Bilateral somatosensory evoked potentials of normal amplitude and with both middle- and long-latency waves; nonconvulsive status epilepticus on the upper side (**a**) and a low-voltage theta and delta rhythm at the lower side (**b**)

The cortical generators of N20 are located in the territory of the middle cerebral artery. A flow reduction below the electrical compromise threshold produces desynchronisation of the activity of the cortical neurons and reduction in the number of functional neurons with a reduction in amplitude.

Numerous studies propose using the N20 parietal amplitude as the diagnostic criterion of cerebral hypoperfusion [5, 12]. It is believed that the latency of SEPs is less sensitive with respect to amplitude in the case of reduced CBF because the metabolic requirement of the white substance (axonal) is less than that of the grey substance (neuronal bodies) [13]. Nonetheless, the CCT (central conduction time) is always measured: this variable reflects electrical conduction between the spinal medulla, the trunk, and the other subcortical hemispherical areas. The significant values are a reduction in N20 amplitude of greater than 50 % and an increase in the CCT of 1 ms [14] or 20 % relative to the baseline value [15].

Both anaesthesia and hypothermia induce a reduction of cerebral metabolism during ECMO and influence brain function. Hypothermia and anaesthesia bring about a gradual, symmetrical change in the EEG and, at temperatures below 30°, in SEP as well. Moderate and mild hypothermia (body temperature over 30 °C) is associated with a reduction in EEG amplitude and frequency. The EEG becomes isoelectric at 22–25 °C [16].

The SEPs react to steady-state hypothermia with an increase in latency and amplitudes of the peripheral and cortical potentials at temperatures over 30°. Below 28–30°, the SEP amplitude reduces [17]. The N20 and P14 components of the SEP can disappear between 15–26 °C and 15–20 °C nasopharyngeal temperature, respectively [16, 17].

Most of the anaesthetic agents cause similar effects in the cortical EEG and SEPs, with the exception of ketamine. These anaesthetic drugs initially cause an increase in the speed of the EEG tracing, which consists of disappearance of the α -rhythm and appearance of a β -rhythm, followed by gradual synchronisation and postero-frontal slowing with subsequent appearance of θ - and δ -rhythms. Increasing the dose of anaesthesia appears as a burst suppression pattern followed by a gradual increase in the isoelectric period until the isoelectric pattern emerges.

Generally the effects of total intravenous sedation on the cortical SEPs, expressed by increased latency and reduction in amplitude, are irrelevant. Opiates may cause slowing of the EEG and the appearance of δ -waves at high amplitudes; the effect on the SEPs, however, is negligible.

Finally, curarisation does not affect the neurophysiological electrical signals; on the contrary, it may bring about an increase in SEP amplitude due to a better signal-to-noise ratio caused by the removal of muscular artefacts.

In addition to standard clinical examination, SEPs improve the accuracy of neurological prognosis of comatose patients from multifactorial etiopathogenetics [18]. Regarding cardiac arrest and therapeutic hypothermia, it has been shown that a multidisciplinary approach composed of the Glasgow Coma Scale (GCS), patient's pupil light reactivity, corneal reflexes, serum neuron-specific enolase, and short-latency somatosensory evoked potentials (N20/P25) improves the accuracy of neurological prognosis [19]. Indeed, the bilateral absence of the early cortical SEP (i.e. N20/P25) has a high predictive value for adverse outcomes such as death or survival in a vegetative state. However, the presence of N20/P25 is not sensitive enough to

predict a good neurological outcome [18]. It is well established that only event-related evoked potentials (i.e. P300) and the presence of middle-latency cortical somatosensory evoked potentials (MLCEP) strongly correlate with a favourable neurological prognosis in patients affected by severe brain injury [20, 21].

The appearance of MLCEP can be produced by an electrical stimulation on the median nerve, because the SEP responses can reflect a more integrated cerebral processing of pain that includes primary and secondary somatosensory cortices: the insular, anterior cingulate, and prefrontal cortices [22].

Pain-related MLCEP may be a measure to predict good neurological outcomes in comatose patients, as demonstrated by previous studies without a pain-related method [23]. Given that only high-intensity stimulation would generate MLCEP, this method allows the detection of the quiescent brain network in the ischaemic penumbra and represents a dynamic test of brain availability; it can be considered a sort of neurophysiological GCS with which the clinicians can evaluate the brain's reactivity to painful stimulation [24]. Interestingly, this method might also be a useful tool to evaluate brain connectivity in patients without normal EEG patterns (e.g. the NCSE).

SEP is a stable signal, is reproducible, and is more resistant to temperature changes, anaesthesia changes, and electrical interference. It also gives information on subcortical structures. SEP provides information on the function of the somatosensory area and, indirectly, on the rest of the parenchyma perfused by the middle cerebral artery. Moreover, exploring neurophysiological reactivity with the painful stimulation gives the physician the chance to gain information on brain function with an isoelectric EEG trace.

The neurophysiological evaluation also provides the possibility of testing other brain functions such as motor, acoustic, and visual, which can contribute to a better definition of the neurological prognosis.

34.3.3 Continuous Brain Function Monitoring

Simultaneous and continuous monitoring of EEG and SEPs has considerable value because their modifications rapidly direct the physician towards more aggressive clinical management [25]. For example, continuous EEG is useful for the diagnosis and treatment of nonconvulsive seizures and status epilepticus, whereas continuous SEPs are more able to indicate the occurrence of loss of somatosensory integrity and brain connectivity in short, middle, and long latency. Continuous EEG/SEP monitoring is unfortunately still lacking in the armamentarium of anaesthesiologists and intensive care physicians, although the majority of the interventional and anaesthesiological procedures performed have an impact on the nervous system.

34.4 Neurosonology Monitoring of Cerebral Blood-Flow Velocity and Microembolic Signals

Transcranial Doppler is the only available method for continuous evaluation of changes in brain haemodynamics in real time, allowing supplementary detection of brain emboli. A sudden drop in peak velocity or loss of the spectrum indicates

conditions of altered perfusion, with a direct causality relationship. An increase in cerebrovascular resistance during ECMO detected with a reduction in diastolic velocity of brain blood-flow velocity may indicate increased intracranial pressure [26, 27].

Ultrasounds are very sensitive in identifying the presence of emboli in the vascular lumen. Patients treated with ECMO can suffer from brain and systemic gas microembolism because air can enter the circuit through the central venous lines; this phenomenon occurs at high flow when all blood is shunting from the lung [28]. The current extracorporeal oxygenator and minimally invasive circuits are less efficient in removing air microbubbles from the extracorporeal circulation, as also experienced during extracorporeal circulation during cardiac surgery [29]. For this reason, maximum care is required in setting and managing the infusion lines during ECMO. The interposition of an air filter device between the intravenous catheter and the infusion lines can prevent this dangerous occurrence.

34.5 Monitoring of Cerebral Metabolism

Brain oxygen saturation can be carried out with either invasive or non-invasive methods, both of which call on continuous infrared spectroscopy; the difference in the absorption spectrum between total haemoglobin and oxygenated haemoglobin provides an estimate of oxygen saturation. With the invasive approach, this measurement is obtained from a sensor located at the end of a catheter positioned in the jugular bulb. With the non-invasive method, an infrared source is positioned at the surface of two adhesive patches placed on the scalp. The sensor proximal to the source picks up the infrared light reflected primarily from the skin and bone, while the more distal sensor receives the light reflected from a sample of brain tissue measuring 1 cm^3 [30, 31]. Because the blood in the brain tissue is 75 % venous, the differential signal provides an estimate of the venous amount of brain oxygen saturation. NIRS has a possible limitation in old patients with brain atrophy because of the low-resolution depth.

While NIRS is bilateral on the frontal lobe, the SjO_2 is monolateral, and it is still an open question to identify the dominant internal jugular vein (which in most individuals is the right jugular). Among the methods proposed for identifying this is the analysis of the size of the jugular foramen lacerum by a CT scan. Moreover, cerebral venous dominance can be obtained by evaluating the highest decrement in the diastolic velocity of the brain blood flow caused by selective compression of the right and left jugular veins.

The metabolic methods (NIRS and SjO_2) for cerebral oxygen saturation reflect the balance between brain oxygen availability and demand. Brain oxygen availability depends on CBF and arterial oxygen level. Because the uncoupling between cerebral oxygen demand and supply is one of the causes of neurological damage, cerebral oxygen saturation measurement is an essential tool for evaluating proper perfusion of the brain tissue; this methodology is also very feasible during ECMO. Brain ischaemia conditions may come about from the combined presence of the following situations: hypotension below the self-regulation limit,

anaemia, arterial desaturation, low PaCO₂ levels, hyperthermia, and cerebral vasoconstriction.

Because the absolute values for regional cerebral oxygen saturation are influenced by many variables, the normal range has not been defined; it is viewed as a cut-off level of 40 % or a 25 % change from baseline values [32]. The finding of cerebral desaturation of less than 40 % with NIRS [33] or less than 50 % with SjO₂ [34] is associated with brain ischaemia. A normal SjO₂ does not guarantee that there are no regional cerebral ischaemias, but a low SjO₂ definitely indicates global ischaemia, focal ischaemia, or both.

34.6 Conclusions

Neurological monitoring during ECMO allows for maintaining the brain's haemostasis. Its functional integrity is vital to patient outcomes and quality of life. EEG and SEP are the most informative neurophysiological tests, and they represent the natural extensions of the neurological clinical evaluation; both have a major prognostic role in acute neurological dysfunction. Their combined use is a unique example of dynamic brain function monitoring.

Transcranial Doppler visualised brain blood-flow velocity and brain vascular resistance provide indirect information on intracranial pressure. TCD is also important in detecting the possible risk of microembolic injury during total extracorporeal supply. Metabolic methods like NIRS and SjO₂ give the chance to monitor the oxygen extraction, targeting the systemic blood flow, oxygenation, and systemic vascular resistance.

The complexity of the ECMO patient and the capabilities of current technologies often make it unfeasible to evaluate brain function, blood flow, and oxygenation simultaneously. In current practice, it is more feasible to perform continuous monitoring with NIRS, while SEP, EEG, and TCD should, in our opinion, be performed at fixed intervals or when the patient's clinical condition changes.

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Monitoring the ECMO Patient: The Extracorporeal Circuit

35

Stefano Isgrò, Francesco Mojoli, and Leonello Avalli

35.1 Introduction

During ECMO, extracorporeal circuit-related adverse events must be carefully monitored, being acute ECMO failure a potentially life-threatening event. ECMO circuit failure requires emergency change-out [1–3], which is possible only by temporarily stopping the treatment, thus exposing patients to further harm [4, 5].

Extracorporeal circuit is composed of cannulae, tubing, a pump, and an artificial membrane lung (ML). Each part of the circuit can break or fail, thus potentially exposing patient to serious side effects. In this chapter we will review major ECMO technical complications and monitoring methods. For a full explanation of different ECMO techniques and materials, we remand to specific chapters in this book.

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35.2 ECMO Failure

ECMO circuit failure, especially during prolonged use, is not an uncommon occurrence in ECMO centres' ICUs [3, 6]. Although every part of the circuit may break or fail, critical parts of the circuit are certainly ML membranes and circuit/pump coupling sites.

35.2.1 ML Failure

Typically modern ECMO treatment fails due to critical narrowing or occlusion of artificial exchanging sites (i.e., embolisms or thrombosis). As ECMO technique exposes blood to contact on artificial surfaces, this interaction leads to the recognition of foreign material surfaces with protein body inflammatory and coagulation system activation [3, 7]. Depending on the charge and composition of the exposed surface, protein deposition and denaturation, as well as thrombin production, occur. Parenteral continuous anticoagulation is thus required to prevent and delay coagulation system activation, being difficult to find the equilibrium between excessive and insufficient anticoagulation (i.e., bleeding vs. circuit or patient thrombosis) [7]. When anticoagulation is not optimal, "circuit coagulation activation" occurs, precipitating "consumption coagulopathy" with blood coagulation factor level drop (especially fibrinogen and platelets), fibrinolytic system hyperactivation, and bleeding (Fig. 35.1) [7].

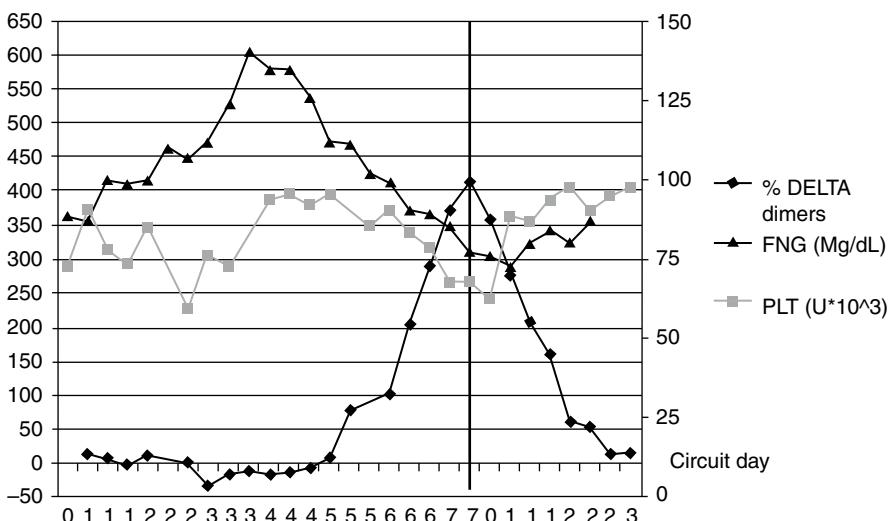


Fig. 35.1 Time course of platelets, fibrinogen, D-dimer % change from baseline between ML change-outs (black vertical lines) during a prolonged VV ECMO treatment, showing "circuit coagulation activation"

A significant technological improvement in MLs has been achieved in recent years, with the transition from silicon non-microporous membrane MLs to microporous hollow-fiber MLs. The latter allows highly efficient gas exchange, reduction in transmembrane pressures, and low priming volume, but plasma leakage through microporous fibers frequently occurs, reducing gas transfer rate. More recently polymethylpentene hollow-fiber MLs have eliminated this problem [4], allowing more longer treatments, reducing the need for circuit change-out. Anyway, even with polymethylpentene MLs, progressive clot formation with partial to total occlusion of blood path and loss of gas-exchanging surface is still an unresolved problem (Fig. 35.2) [2, 6].

35.2.2 Circuit/Pump Failure

Though more resistant materials and more biologically compatible inner circuit coatings have been developed, hemocompatibility is still limited, and careful monitoring of the ECMO system is required. Each part of the circuit must be inspected frequently in search of blood clots and deformities of tubing, especially where blood flow is more turbulent as at fittings, stopcocks, and cannulae. Expected complications may be different depending on the pump technology employed and on patient population (adult vs. pediatric); the most popular technologies are the roller pump, actually more diffused for children [5], and the centrifugal pump. The overall complication rate is not significantly different [8], with a significative difference in hemolysis (but not in in-hospital survival) in favor of roller pumps among children [5]. Roller pump specific complications are raceway or circuit break and, consequently, air embolism; centrifugal pumps instead are specifically exposed to pump head/pump engine decoupling, consequently stopping treatment and thrombosis. Alternative technologies such as nonocclusive and miniaturized pumps have been



Fig. 35.2 Black arrows showing clots in the pump head after a circuit change-out

developed [8]. Some centres use two pumps/MLs running in parallel: in case of failure of an ECMO system, the second ECMO allows a full support to the patient. Other centers have a primed ML circuit always ready to be implemented [8]. Ideally whole circuit or ML change-out should be performed electively to decrease morbidity due to circulatory lack of assistance (VA ECMO) or oxygenation/ CO_2 removal (VV ECMO) during change-out procedure. Up to now circuits are changed according to clinical nonstandardized criteria. Major clinical criteria may be summarized in:

1. Circuit coagulation activation
2. Gross thrombosis of circuit components
3. Technical failure of the circuit/ML

35.3 Monitoring Techniques

35.3.1 Blood Flow and RPM

In order to monitor energy/mechanical failure of the ECMO pump, rotation per minute (RPM, available both for roller and centrifugal pumps) is always continuously displayed and alarmed. Monitoring RPM is of particular importance on roller pumps, RPM being directly related to blood flow (when occlusion is accurately set and circuit and raceway are intact); when a centrifugal pump is employed, for a set RPM, blood flow is mainly driven by flow resistance of the ECMO circuit (cannulae, tubing, ML) and by patient fluid status: therefore, in case of low-volume state and high RPM, blood flow may abruptly fall, eventually leading to suctioning of venous wall and/or ECMO treatment interruption. This occurrence often leads to blood–pump head decoupling and requires a special emergency procedure to restart ECMO. Close flow monitoring and alarming are thus needed. According to different technologies, companies developed specially modified fittings where flowmeters may be applied on the circuit.

35.3.2 Anticoagulation

As seen above ECMO circuits still require adjunctive anticoagulation to avoid circuit component thrombosis. Adequate anticoagulation level during ECMO is the balance between circuit/patient thrombosis and patient bleeding; finding the optimal level could be challenging as it is not absolute and varies according to circuit and patient status [9] (i.e., preexisting coagulation disorders, ECMO circuit and treatment duration, sepsis). As bleeding and thrombosis are still the principal causes of morbidity and mortality during ECMO [7], strict anticoagulation monitoring is essential.

ECMO anticoagulation is generally obtained with unfractionated heparin (UFH), which is the drug of choice because of a favorable pharmacological profile: in fact it has a parenteral, fast-onset, rapidly reversible effect and is an economical and a

widely diffused drug. Despite this, heparin is not ideal, as it has a non-predictable anticoagulant effect, thus requiring close monitoring and frequent variations in dosage. Moreover, anticoagulant effect could not be accurately monitored, and consequently each test requires careful interpretation (see below), sometimes making clinical management difficult [7, 10]. Unfractionated heparin acts by binding with antithrombin III (ATIII); hence, as hepatic ATIII production may be impaired, ATIII level must be frequently monitored and kept constant. Finally, it is associated with heparin-induced thrombocytopenia (HIT) [11, 12].

Heparin anticoagulation can be monitored at bedside with activated clotting time (ACT), point-of-care activated partial thromboplastin time (aPTT), and viscoelastic tests (VET) or can be monitored with routine (aPTT, D-dimers) or special (heparin plasma level – antiXa activity) coagulation lab tests.

aPTT is the standard test to measure heparin anticoagulation; it measures plasma coagulation pathway in-vitro at 37°C temperature. Accordingly, interactions between platelets and other blood cells with soluble factors are not tested, so aPTT test reflects only a small fraction of the thrombin produced during the coagulation process [13].

ACT [14] is a widely diffused test among ECMO centers [9], being classically employed in the cardiopulmonary bypass setting, where high dose of heparin and point-of-care test are required. ACT can also be used for lower dose of heparin: a sample of fresh whole blood is inserted into a warmed cuvette where coagulation is activated by a negatively charged activator (celite or kaolin). ACT measures the seconds needed for the blood to start clotting. Anticoagulation is kept to obtain a value between 180 and 220 s. It is affected by sepsis, D-dimers, platelet dysfunction, thrombocytopenia, hypofibrinogenemia, and hypothermia.

Correlation between ACT and aPTT is poor [9, 14]; therefore, in clinical decision making, factors influencing both tests must be considered.

Some centers employ viscoelastic test as an adjunct to anticoagulant therapy monitoring, being a test extremely sensitive of heparin activity variation. Nevertheless, experience in this application of thromboelastography/thromboelastometry is still limited [7].

This is the anticoagulation monitoring protocol that we follow in our centre:

1. Platelets
 - (a) Platelet levels are checked every 12–24 h.
 - (b) Platelets are administered when lower than 50,000 units/mm³.
2. ATIII
 - (a) Plasmatic ATIII level checked daily until stable value with (or without) replacement and then every 2–3 days.
 - (b) Replace as needed to obtain a value >100 %. Dosage is decided according to the formula: unit to be administered = weight (kg) × [ATIII desired (%) – ATIII measured (%)]/1.4.
3. ACT
 - (a) Checked after 1 and 3 h after heparin boluses and then every 6–8 h. Target result is decided by integration of ACT with other coagulation tests.

4. Standard coagulation tests

- (a) aPTT, fibrinogen, and D-dimers checked three times a day. aPTT value is kept between 50 and 60 s (ideally aPTT 1.5–2 times the patient's baseline), and FNG above 200 mg/dL.
- (b) Ionized calcium is obtained with ABG analysis and is kept within physiological range.

5. Thromboelastography

- (a) Upon clinical decision and simultaneously with standard coagulation tests to address baseline coagulation (whole kaolin + heparinase TEG tracing shape) and *R* time value in the kaolin tracing.

Case series with new parenteral direct thrombin inhibitors argatroban [15–17] and bivalirudin [18] have been published, but experience with these drugs during ECMO is still limited.

35.3.3 Pressures

Circuit pressure monitoring may be mounted onto the ECMO circuit at different sites, representing an easy and effective alarming and information system about both roller pump and centrifugal pump ECMO performances. To monitor pressures and to draw blood, manufacturers provide preassembled or spare fittings with a side port (Luer-lock connectors). Monitoring sites vary through institutions according to the age of the ECMO patient [4] and to local practices and protocols. Commonly used monitored sites are:

1. Two sites on either side of the ML (pre-ML and post-ML), providing information about variation in pressure drop and blood flow resistances through the oxygenator. An increase in pressure drop suggests ML thrombosis (Fig. 35.3) [2]. Resistance of blood flowing through the oxygenator may be computed according to the following formula: $R = (pin-pout)/BF$, where pressures are expressed in millimeters of mercury and BF in liters per minute ($R = \text{mmHg/L/min}$). Each manufacturer provides product-specific performance charts comparing resistances at different blood flows.
2. Inlet venous line, giving negative pressure readings of blood suctioning from the patient, thus monitoring oversuction (centrifugal pump ECMO) [4]. Excessive negative pressure applied to the venous system may actually result in bubble formation (cavitation) and hemolysis [5], suctioning of vena cava–right atrium wall (endothelial damage), and air embolism [3]. To avoid this occurrence, a pump speed control system is employed on roller pump ECMO, servo-regulated by a transducer mounted onto the aspiration line.
3. Pressure measured at the patient inlet, “system pressure” (roller pump ECMO).

35.3.4 ML Gas Transfer

The primary task of artificial membrane lungs (MLs) is the total or partial support of the native lung function by O_2 transfer to and CO_2 removal from blood. The Association for the Advancement of Medical Instrumentation (AAMI)

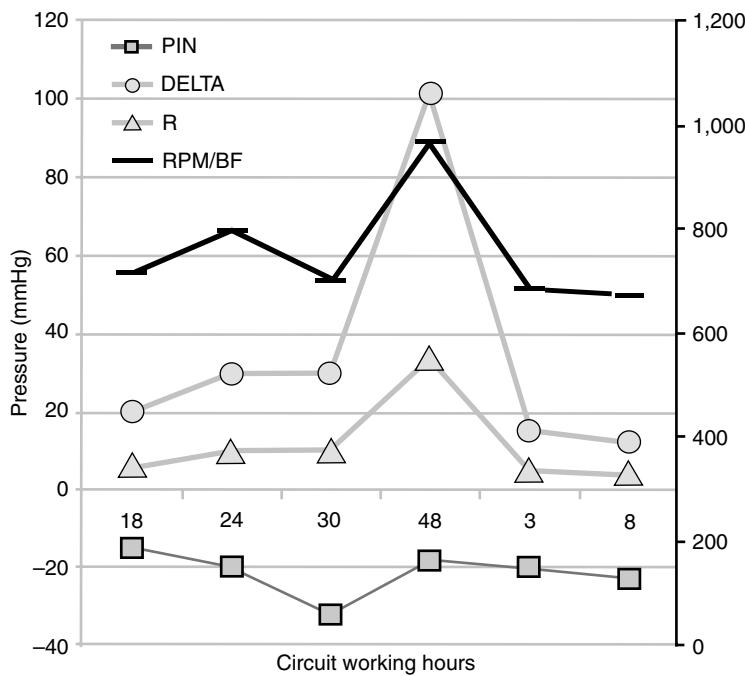


Fig. 35.3 Time course of circuit pressures (*Pin* pressure measured before centrifugal pump, *DELTA* difference of pressures measured before and after ML blood line, *R* resistances across ML, *RPM/BF* centrifugal pump rotations per minute/ECMO blood flow) showing a case of urgent ML change-out due to a rapid increase in resistances across ML. D-Dimers and other coagulation index of “circuit activation” were all in the normal reference range

standards defined the minimum requirements for clinical use of MLs: 45 ml of O₂ transferred and 38 ml of CO₂ removed per liter of blood flowing through the ML. This means that MLs are able to turn normal venous blood into normal arterial blood in terms of both O₂ and CO₂ content, whatever the blood flowing through (up to the maximum flow rate of single devices).

Anyway, the performance of ML can deteriorate over time, and sometimes it happens abruptly. As in the native lungs, abnormalities of gas exchange in the artificial membrane lungs can be described and quantified by Riley’s three-compartment model: ideal, shunt, and dead space compartment [19]. Displacement of hollow fibers in MLs is studied in order to maximize gas exchange by optimal matching of gas and blood flows. Anyway, in hollow-fiber MLs the ideal compartment is always associated with a variable shunt compartment (perfused but not ventilated) and dead space compartment (ventilated but not perfused). When the shunt compartment was evaluated during cardiopulmonary bypass in the cardiac surgery setting, it ranged 10–30 % in modern hollow-fiber MLs [20–22]. In Figs. 35.4 and 35.5 shunt and dead space compartments in two cases of extracorporeal lung assistance with a high sweep gas flow (10 l/min) are shown: early after the start of the extracorporeal

Fig. 35.4 Monitoring oxygen transfer in the artificial membrane lung: time course of shunt and pO_2/FO_2 ratio. Shunt is already present at the very beginning of the extracorporeal assistance and increases with time, indicating progressive loss of O_2 transfer performance in the ML. In this particular case, pO_2/FO_2 ratio mirrors almost perfectly the behavior of shunt

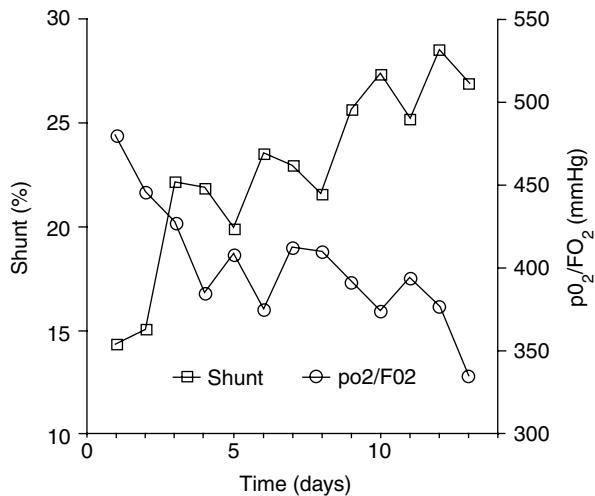
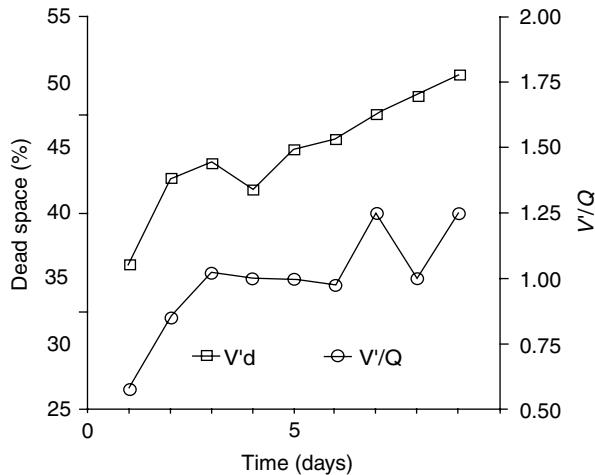


Fig. 35.5 Monitoring carbon dioxide removal in the artificial membrane lung: time course of dead space and V'/Q ratio. Dead space is already present at the very beginning of the extracorporeal assistance and increases with time, indicating progressive loss of CO_2 removal performance in the ML. In this particular case, V'/Q ratio mirrors almost perfectly the behavior of dead space



assistance, shunt and dead space were already present and accounted for 15 % and 35 % of blood and gas flowing through the ML, respectively.

The further loss of ML performance during prolonged use can be due to both fluid accumulation in the hollow fiber lumen and clot formation on the blood side of the hollow fiber surface.

The availability of polymethylpentene (PMP) hollow-fiber MLs has dramatically reduced the occurrence of significant plasma leakage [4]. Anyway, slow filtration of plasma water through the PMP microporous membrane is still present, and sometimes fluid accumulation in the fiber lumen occurs. When the gas flow is impeded by fluid accumulation in a significant proportion of fibers, ML performance accordingly decreases due to a “shunt effect.” In these cases, patency of hollow fibers can be reestablished by gently purging them with a brief period of high sweep gas flow.

To avoid this problem, recently developed devices for extracorporeal lung support are provided with a periodic purge function.

Despite the use of biocompatible inner circuit coating and systemic anticoagulation, thrombotic and cellular deposits on the outward surface of fibers occur, with a rate that is not easily predictable [23]. These deposits increase the resistance to blood flow and the diffusion path of the gas exchanger fibers, leading both to shunt and to dead space formation. Actually, pseudomembranous deposits – whose thickness can almost reach the thickness of the hollow-fiber wall – may completely impede gas exchange while blood flow is still maintained (shunt effect), whereas extensive clot formation around fibers may completely stop blood flow while gas is still flowing in fibers' lumen (dead space effect).

Monitoring the ML gas exchange function is therefore mandatory in prolonged respiratory and/or circulatory extracorporeal assistances: patient's metabolic demands, especially in case of large/awake/critically ill subjects, could eventually not be assured by an ML with a significant loss of performance. Monitoring ML may accordingly help in identifying the timing for a scheduled, elective replacement of the extracorporeal circuit, thus avoiding emergency and dangerous procedures.

Finally, monitoring the ML provides useful information for the management of the extracorporeal assistance: the knowledge of the actual contribution of the ML to gas exchange may help in identifying and correctly treating the cause of blood gas abnormalities and, in the venovenous ECMO setting, may guide the weaning procedure.

Both O₂ transfer and CO₂ removal should be monitored, because both the functions can deteriorate with time in MLs and, to note, not always with the same rate. An example of this is Fig. 24.3: the first displayed ML was replaced because of progressive and significant deterioration of CO₂ removal while O₂ transfer was still satisfactory; in the second ML, decay of CO₂ removal and of O₂ transfer went on instead in parallel.

In clinical practice, the simplest way to monitor oxygen transfer is to measure the O₂ partial pressure (pO₂) in the blood coming out the device (usually at the same outlet site of Pout measurement) in relation to the O₂ fraction of sweep gas flow (FO₂): this way, the pO₂/FO₂ ratio of the ML can be calculated. Alternatively, once two simultaneous blood samples at the ML inlet and outlet are obtained, the percentage of shunt can be formally computed as shown in Fig. 35.6.

Generally, pO₂/FO₂ and shunt % provide the same information on ML status: in Fig. 35.4, time course of these parameters is almost specular, the progressive decrease of pO₂/FO₂ corresponding to a simultaneous increase of shunt % in the ML. But this is not always the case, because pO₂/FO₂ depends also on inlet blood O₂ content. An example of abrupt and significant drops of pO₂/FO₂ not associated with increased shunt % is displayed in Fig. 24.4. High metabolic demands, as during shivering, may favor low venous (inlet) blood O₂ saturation and low pO₂/FO₂ despite stable shunt %, i.e., without any evidence of ML loss of performance.

In order to counteract the decay of CO₂ removal capacity in the ML, the sweep gas flow (SGF) should often be progressively increased up to the maximum value indicated by the manufacturer (usually 10–12 l/min). Accordingly, the ventilation/perfusion (V'/Q) ratio of the ML (i.e., the sweep gas to blood flow ratio)

Shunt membrane lung

$$\frac{Q_s}{Q_{CEC}} = \frac{(C_{cap}O_2 - C_{OUT}O_2)}{(C_{cap}O_2 - C_{IN}O_2)}$$

$$C_{cap}O_2 = 0.0031 \times P_AO_2 + 1.39 \times Hb \times Sat_{TC}$$

$$P_AO_2 = (P_{ATM} - P_{H2O}) \times FiO_2 - P_aCO_2/RQ$$

$$Sat_{TC} = X - (HbCO + MetHb)$$

Fig. 35.6 Shunt definition: CEC means extracorporeal circulation, C means concentration, $C_{cap}O_2$ means capillary (ideal) O_2 concentration, and RQ means respiratory quotient, x is 1, 0.99, or 0.98 if PaO_2 is above 250 mmHg, between 150 and 250, or below 150, respectively

progressively increases: this parameter can be used in clinical practice to easily and continuously (even if grossly) monitor the CO_2 removal function. To note, CO_2 removal depends on SGF in a nonlinear manner [24]: when the gas flow is progressively increased, the gain in CO_2 removal progressively decreases and, at gas flows greater than 10 l/min, almost vanishes (see also Figs. 24.1 and 24.2 for the relationship between SGF and CO_2 removal). Figure 35.5 shows the time course of the ML V'/Q ratio during prolonged extracorporeal support: the increase of dead space in the ML is coupled with and counterbalanced by a corresponding increase of V'/Q . Anyway, it should be underlined that V'/Q ratio is directly influenced by an ECMO setting – the sweep gas flow – that in turn depends also on clinical targets (arterial blood CO_2 and pH) and on patient's CO_2 production. This means that the V'/Q ratio can change for reasons other than impaired CO_2 removal in the ML.

Alternatively, formal computation of dead space % in the ML can be obtained as follows:

$$\text{Dead space \%} = 100 \times (pCO_2, \text{blood} - pCO_2, \text{gas}) / pCO_2, \text{blood}$$

where pCO_2, blood and pCO_2, gas are the CO_2 partial pressures in the ML blood and gas outlet, respectively. Recently developed devices for extracorporeal lung support are provided with an integrated capnometer at the gas outlet port, thus permitting continuous monitoring of pCO_2 , gas and extracorporeal CO_2 removal.

In conclusion, for monitoring gas exchange in the MLs, pO_2/FO_2 and V'/Q ratio are easy to obtain and can be used for trends, whereas shunt and dead space computations are more cumbersome but reliable parameters. At our institutions, we measure shunt and dead space of the ML at least daily and whenever clinics dictate the need for an accurate assessment of the ML performance.

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Part VI

Complications of ECMO

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Due to its technical complexity and the critical illness of patients suited for its use, ECMO has a high potential for complications [1]. Most of these can result in life-threatening conditions able to change the patients' outcome. For this reason, a correct prevention and an early recognition of symptoms and signs can help to reduce the incidence of adverse events.

Complications can be related to either circuit components or patient conditions.

36.1 Circuit-Related Complications

36.1.1 Blood Clots in the Circuit and Thromboembolism

Because of blood-surface interaction, clots can form in the circuit and originate embolic events with potentially devastating consequences [2].

Thrombi can appear at almost any point in the circuit (oxygenator, pump head, tubing) (Figs. 36.1 and 36.2).

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Fig. 36.1 Clot formation on the venous side of the membrane lung

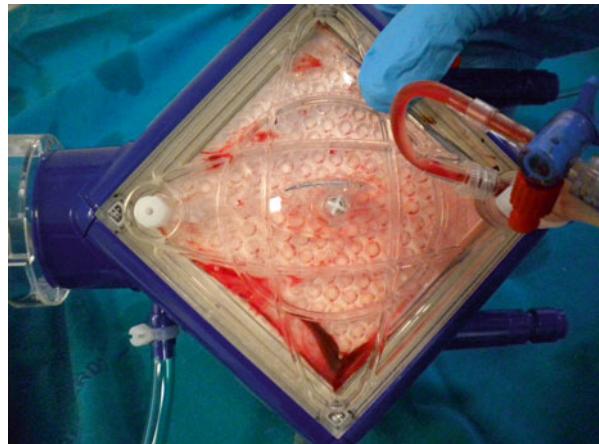


Fig. 36.2 Clots in the tubing



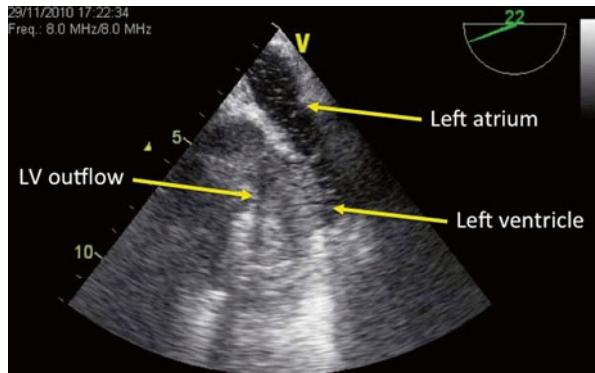
36.1.2 Gas Embolism

Gas embolism is related to the capacity of the centrifugal pump to generate high negative pressure between the drainage cannula and the pump head. In case of air entrainment in this part of the circuit, a massive gas embolism can occur.

36.1.3 Circuit Fractures

Fissures or breakage can occur in virtually every component of the extracorporeal circuit. Those may be large, causing major blood loss, or unapparent and difficult to detect. When on the venous site of the circuit, massive air aspiration and consequent embolism can occur as a result of high negative pressure generated by the centrifugal pump (Fig. 36.3). All fractures prompt substitution of the part or of the entire circuit depending on the site of rupture.

Fig. 36.3 Massive air embolism in the left ventricle



36.2 Patient-Related Complications

36.2.1 Cannulation Vascular Complications

Cannulation may pose difficulties related to both anatomical reasons (size and stenosis of vessels, particularly arteries, anatomical variations, previous surgeries, morbid obesity) and clinical conditions of the patient (absence of pulsatility during low-flow states or cardiac arrest, vasoconstriction). These may – even if this is quite rare in our experience – make cannulation impossible unless a central approach is readily attainable.

Vascular complications can occur at the time of cannulation and are more frequent with the percutaneous approach as compared to the surgical approach.

36.2.1.1 Vascular Access Complications

Arterial cannulation, particularly when performed with a percutaneous approach, may lead to serious complications.

Perforation of the posterior wall of the vessel may cause uncontrollable bleeding with ensuing inadequate perfusion. This may in turn lead to compartmental syndrome or retroperitoneal hematoma, depending on the site of vascular injury. This may also result in arteriovenous fistula or pseudoaneurysm formation, which may require surgical repair immediately or at a later time (Fig. 36.4).

Guidewires and dilators can also cause arterial dissection or the creation of false ways leading to extravascular cannula positioning and consequent inability to circulate blood.

All these complications require close monitoring and prompt interventions. Some tricks to prevent such complications are outlined in Chap. 37.

36.2.1.2 Leg Ischemia

Leg ischemia is a risk with femoral arterial cannulation (Fig. 36.5). In case of peripheral VA ECMO, the return cannula in fact is typically placed into the femoral artery and the drainage cannula into the contralateral femoral vein. The insertion of a distal perfusion cannula, which is connected to the return tubing via a T-connector,

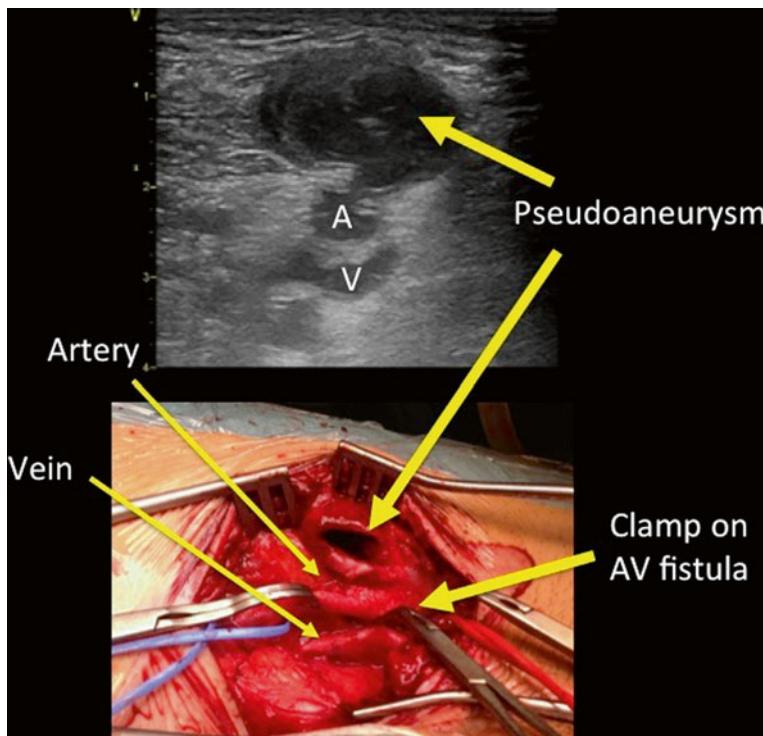


Fig. 36.4 Iatrogenic arteriovenous fistula of the femoral vessels with voluminous pseudoaneurysm of the femoral artery

should always be considered (Fig. 36.6). It is easier to place the distal perfusion cannula before the return cannula is inserted in the femoral artery to avoid the insertion in condition of reduced pulsatility. In case of emergency VA ECMO insertion while the return cannula insertion has been prioritized, a surgical cutdown could be performed in order to place the perfusion cannula instead of percutaneous insertion.

36.2.2 Bleeding

Bleeding is one of the most common complications during ECMO because of systemic anticoagulation and platelet dysfunction, which results from contact and shear stress associated activation. For this reason even conventional routine procedures (i.e., endotracheal suctioning, nasogastric tube positioning, urinary catheterization) can lead to uncontrollable bleeding, requiring further intervention and alteration in the anticoagulation regimen.

Fig. 36.5 Peripheral ischemia in the cannulated leg



Fig. 36.6 Peripheral perfusion cannula in the cannulated leg



A continuous monitoring of coagulatory status (ACT, aPTT, PT, and PLT count, TEG/ROTEM) is essential especially prior to invasive procedures to reduce the bleeding events.

36.2.2.1 Surgical and Cannulation Site Bleeding

Cannulation sites represent the most frequent source of bleeding, especially in the setting of surgical cannulation. In this case a slow oozing around the cannula can be related to disruption of small vessels and managed with compression or redressing. Sometimes a resuturing or modification of coagulation protocol is required. The extent of bleeding is generally less in case of percutaneous cannulation with Seldinger technique. Compared to venous cannulation, arterial cannulation is related to higher risk of bleeding. Whenever bleeding occurs from cannulation sites, it is good practice to assess the correct positioning of the cannula before taking any intervention, in order to exclude malposition and prevent accidental decannulation.

In one series of more than 400 adults placed on ECLS for severe ARDS refractory to all other treatment, cannulation site bleeding occurred in 31.4 % and surgical site bleeding in 26.7 % of patients [3].

In case of central ECMO, cannula site bleeding represents a surgical problem and requires careful monitoring and prompt surgical revision in order to avoid serious complications such as tamponade.

36.2.2.2 GI Bleeding and Airway Bleeding

In this delicate scenario of hemostasis and anticoagulation, bleeding from the mucous membrane as in the nasopharynx, trachea, stomach, rectum, and bladder commonly occurs even with minor trauma. Routine procedures related to patient care such as suctioning and bronchoscopy or urinary catheter insertion can trigger bleeding often difficult to control in these areas.

GI bleeding can occur from esophagitis, gastritis, duodenal ulcer, or other sources. Endoscopy is often able to recognize the precise source of bleeding, and angiography should be considered if further investigation is needed. ECLS patients should be treated in the same way of any patient with active GI bleeding ensuring the correction of the coagulopathy and considering endoscopic procedure when feasible or surgical operation in case of uncontrolled bleeding.

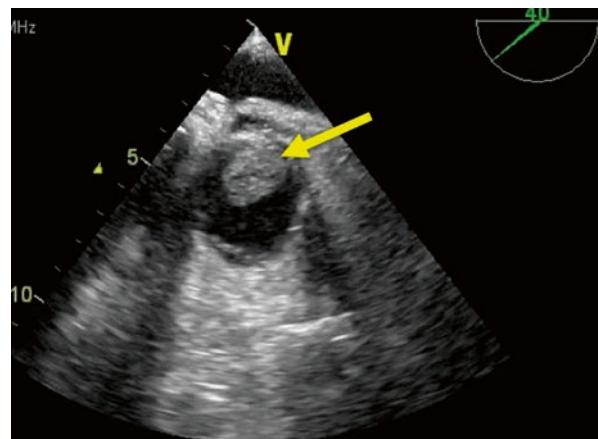
36.2.3 Coagulopathy (Thrombocytopenia, HITT, and DIC)

One of the key points in the ECMO management is the delicate balance between hemostasis and thrombosis that requires constant clinical and laboratory monitoring with replacement of coagulation factors, fibrinogen, and platelets. These aspects are dealt with in Chap. 7.

An expected dilution of blood cells, platelets, and proteins due to the circuit priming with crystalloids occurs when ECLS is established with increased fluid component of the blood and equilibration into the extracellular space causing edema. An anemic state requires furthermore higher pump flow to achieve adequate perfusion and gas exchange, resulting in higher post-pump pressures. For these reasons achievement of adequate hematocrit levels is particularly important in ECLS [4].

Thrombocytopenia is common in ECLS patients. It may be a consequence of the primary disease, drug induced, or caused by blood exposure to the circuit surface.

Fig. 36.7 Thrombus (arrow) in the ascending aorta



The interaction between the blood and the artificial surface causes protein absorption such as fibrinogen and albumin. As this occurs, platelets adhere and create a cascade of events that results in thrombus formation (Fig. 36.7) and activation of the coagulation cascade by the intrinsic pathway, resulting in the release of inflammatory mediators and the production of thrombin [5].

Platelet count can drop as low as 40 % from baseline within the first 4 h of ECLS [6]. The usual practice and the ELSO Guidelines indicate the threshold for platelet transfusions of 80,000 despite different centers indicating a minimum platelet count of 100,000.

Even though the platelet count is over the minimum level (80,000–100,000), the platelet function may be impaired. In this case a kallikrein inhibitor (tranexamic acid or aprotinin) is suggested to improve platelet function if bleeding is a problem [4].

Systemic heparinization has been demonstrated as the gold standard for anticoagulation in these patients, as it is inexpensive, easily titrated, easily monitored at the bedside, and immediately reversed by protamine. Despite these advantages, heparin does not prevent platelet-surface interaction, and furthermore, it can itself cause further platelet activation, dysfunction, and consumption [6].

A rare condition associated with heparin anticoagulation is heparin-induced thrombotic thrombocytopenia (HITT) characterized by multiple white arterial thrombi and platelet count less than 10,000. The assay available for HITT has a very high false-positive rate. If an ECLS patient has true HITT, the platelet count will be consistently less than 10,000 despite platelet infusions. In this case, if there are no other reasons to explain the thrombocytopenia, it is reasonable to use different anti-coagulant such as Argatroban.

Another aspect that can trigger the coagulopathy related to ECLS is hemolysis, suspected if the urine has a pink tinge and verified by plasma Hb measurement (normal plasma hemoglobin should be less than 10 mg/dl). High risk of hemolysis occurs if the pump suction exceeds the blood drainage (high inlet pressures) as a result of high flow rate through a very small orifice or if there is a high level of occlusion in the post-pump circuit. The presence of clots in the pump chamber may enhance this phenomenon [5].

36.2.4 Neurological Complications

The most devastating of these causes is the intracranial hemorrhage, usually fatal. The reported incidence of intracranial hemorrhage varies between 1.6 and 18.9 %. A careful management of anticoagulation with a prompt correction of thrombocytopenia and prevention of renal failure seems to be the factor that can reduce the incidence of this fatal complication, while the duration of ECMO support has not been shown as an independent risk factor [6]. The Extracorporeal Life Support Organization (ELSO) registry reported 2 % of CNS hemorrhage in adult patients requiring cardiac support with an overall survival of 8 % and a rate of 4 % in patients requiring VV ECMO with a higher survival rate (21 %).

In addition to hemorrhage, infarction (1–8 %) and seizures (2–10 %) are common complications. Thromboembolic events can progress to ischemic stroke in different portions of the brain, including frontal lobe, occipital lobe, basal ganglia, and parietal lobe. Clinical seizures can be associated with radiographic evidence of cerebral edema.

36.2.5 Cardiac Complications

Complications within the chest such as cardiac tamponade, LV distention, or pneumothorax can be the cause of further hemodynamic instability and ECMO flow disturbances because of cannula compression or reduced atrial volume. Hypotension and concomitant high (negative) inlet pressure can be related to hypovolemia or suboptimal patient sedation itself, but it is fundamental to exclude any of these complications. Any sudden change of intrathoracic pressure such as tension pneumothorax may constrict the pericardium leading to decreased venous return and decrease of the ECMO flow similar to tamponade physiology. An initial fluid challenge can assess the volume status of the patient as well as an optimization in sedation and paralysis. If no improvement in ECMO flow is noted, imaging such as chest radiograph or echocardiogram is recommended.

The ECMO flow disturbances related to significant intrathoracic pathology have been well described in pediatric population; however, these have not been clearly described in the adult ECMO patients.

A particular problem associated with VA ECMO is the LV distention. An evidence of pulmonary edema on the chest radiograph or edema fluid frothing up the endotracheal tube can be the first manifestation of this problem. A transesophageal echocardiography can confirm the diagnosis identifying a severely dilated LV. The presence of mitral or aortic regurgitation can exacerbate the problem, and an increase in pump flow helps to reduce the pulmonary flow, ameliorating the problem.

LV distention is not a problem exclusively related to central VA ECMO; in patient with peripheral VA ECMO, despite adequate left ventricular unloading, there is still returning blood flow to the left atrium, principally due to the bronchial

circulation. Consequently, if LV contractility is profoundly reduced, we can assist to an increase in left heart pressures resulting in LV distention [7].

The increase in wall stress associated with LV distention not only increases myocardial energy consumption resulting in ischemia but also reduces the likelihood of ventricular recovery.

A surgical or percutaneous LV vent insertion must be performed in these cases.

36.2.6 Infection/Sepsis

ECMO patients are at increased risk of nosocomial infection when compared with other patients in the surgical ICU setting [8].

ECMO patients generally have multiple indwelling catheters, such as pulmonary artery catheters and radial artery catheters, in addition to the cannulae used for the ECMO circuit, with consequentially increased risk of bloodstream infections (BSI).

Considering their prolonged intubation, invasive catheters, and frequent antibiotic therapy, these patients are exposed as well at high risk of ventilator-associated pneumonia.

Usual clinical signs and symptoms associated with nosocomial infections may not be present in these patients making the diagnosis difficult. In particular, fever may be absent due to servo-control of body temperature by the heat exchanger. Broad-spectrum empiric antimicrobial therapy should be instituted early until the results of microbiological cultures become known.

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Lisen Hockings and Alain Vuylsteke

37.1 Patient Selection

No absolute or definitive criteria for patient selection or exclusion exist, and institutions have developed lists of indications and contraindications for ECMO based on their own experiences.

Published criteria vary based on the mode of support [1–3].

When doubt exists about the need for and/or suitability of a patient for ECMO a consensus opinion between experienced ECMO clinicians should be sought.

Issues can arise when ECMO has been started without considering future plans. Sometimes used as a bridge to decision, it is most often a bridge to recovery or another therapy such as an organ transplant.

37.2 Type of Support

It is tempting to consider the use of VA ECMO as a solution to all problems.

For example, patients with respiratory failure can present with profound hemodynamic compromise, perhaps because of hypoxia, acidosis, or extreme settings on the mechanical ventilator. The clinician might be tempted to initiate VA ECMO, either peripherally or centrally.

Central VA ECMO should be very carefully considered, as it requires sternotomy. The positioning and anchorage of the ECMO tubing is critical to allow mobilization of the patient and avoid infection to set in (mediastinitis). A sternotomy is a

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major aggression when other options are possible. It will render future surgery difficult and may influence decision to progress to other form of support.

Peripheral VA ECMO (femoro-femoral) can lead to differential oxygenation, with the ECMO circuit in effect oxygenating part of the body and the native circulation oxygenating another (or not if the lung ability to exchange gas is affected by the disease process). In this situation, a patient can be pink but have profound coronary ischemia! Peripheral VA ECMO is primarily a bridge to decision (such as during e-CPR) or a relatively more permanent form of cardiac support (such as a ventricular assist device or transplant). Complications related to the arterial cannulation are common, including ischemia and dislodgment.

Other configuration of peripheral VA ECMO (such as with the return cannula grafted onto the axillary/subclavian artery) is more likely to ensure adequate cerebral oxygenation (but not necessarily myocardial) [4]. Grafting can in itself cause an issue with disconnection due to continuous shear stress on the suture lines.

The hemodynamic disturbance observed in patients with respiratory failure can usually be sorted with the restoration of the physiological acid–base equilibrium, oxygenation, and decrease in intrathoracic pressures. This can be achieved by both VA and VV ECMO [5].

VV ECMO is relatively less invasive and allows patient mobilization.

Single-stage dual-lumen cannulation will suit some patients and offers the advantages of single-site cannulation. Support of some patients may be hindered by the limitation of blood flow rates when using this cannula [1, 6, 7].

37.3 Insertion

37.3.1 Location of Other Lines

The location of all central venous access (such as central venous lines, dialysis catheters, and pulmonary artery catheters) and arterial monitoring lines needs to be reviewed when contemplating ECMO.

Sufficient time should be made available to resite lines and change infusions prior to establishing ECMO whenever possible.

Team can select to use the ECMO circuit to connect dialysis systems or infusion pumps. This increases the risk of air embolism or infections due to repeated manipulation. Strict protocol and training program must be in place for such practices to be safe.

In VV ECMO, the right internal jugular vein (RIJV) is best situated to allow easy insertion of large cannula. It is the only site that can be used safely with single-stage dual-lumen in the adult patient. We advocate having the RIJV available from the outset as it is safer to resite lines prior to instituting ECMO. If a line is already in place, it should be left in and used as a guide to insert the cannula guidewire, decreasing the risk of puncture.

Concerns have been raised in relation to obstructing cerebral venous drainage when both internal jugular veins are used with large cannula. Positioning the patient

head carefully may help improve this. Assessing patency of the jugular veins before establishing VV ECMO is warranted.

Thrombosis in any of the jugular vein seen prior to cannulation should force the clinician to reassess the risk/benefit of VV ECMO and/or the cannulation location.

Solution would be to limit the VV ECMO support to femoro-femoral cannulation, but efficiency of such system will be lower.

Subclavian insertion of multiple-lumen central venous line should be considered, accounting for the risk of pneumothorax in often unstable patients and subsequent thrombosis. Real-time ultrasound to cannulate the axillary/subclavian vein increases the safety of this approach in patients [8, 9].

A pulmonary artery catheter can measure the pulmonary artery pressure. Thermodilution measurements will be inaccurate as part of the injected solution is likely to end in the ECMO circuit and mixed venous oxygen saturation is not meaningful. Visualization of the pulmonary artery trace allows identification of pulmonary blood flow on those patients on VA ECMO. The usefulness of a pulmonary artery catheter during VV ECMO is dubious.

The presence of end-tidal CO₂ is an alternative means of assessing the presence of pulmonary flow when pulmonary artery catheter is not in situ and the lung can be ventilated.

Cannulation of an artery may lead to distal ischemia, and reperfusion cannula should be considered and inserted in most cases.

Note that the relative venous obstruction from the presence of a femoral venous line can leave the limb at risk of hyperperfusion (if the reperfusion flow exceeds venous drainage). Venous cannulation can be the cause of arterial ischemia by compression.

The decision to rewire an existing line for ECMO cannulation should be undertaken on a case-by-case basis. De novo puncture under sterile conditions will decrease the infectious risk.

A right upper limb arterial line is preferred in patients on peripheral VA ECMO (alternative arterial monitoring sites may miss the early signs of differential hypoxia). Where a right upper limb arterial line is not possible, the saturation probe should be placed on the right upper limb.

If time allows, it is easier to resite the arterial lines prior to commencing VA ECMO support even in the setting of cardiogenic shock (pulsatile flow).

In our view, the use of ultrasounds is mandatory.

Where central veins are being accessed during ECMO support, it is important to remember that the continuous access from the vena cava(e) generates negative pressures that increase the potential for air entrainment and air embolus.

37.3.2 Cannulation Location and Techniques

The portable size of ECMO circuits, associated to increased experience and range of indications, has led to ECMO being used in different hospital locations. Some countries have even experimented with out-of-hospital insertion.

Operator skill set, urgency of support, and available equipment will influence the technique.

Operating rooms, interventional radiology laboratories, and angiography suites offer the advantage of real-time imaging to prevent accidental cannulation of inappropriate vessels (particularly as they occur more distally – e.g., the hepatic vein) and early identification of wire kinking during dilatation.

Combined with real-time ultrasound for percutaneous vessel cannulation, we believe that image intensification is the gold standard technique for ECMO cannulation.

In urgent and emergent situations, cannulation can be performed safely with real-time ultrasound for percutaneous cannulation and transthoracic or transoesophageal echocardiography. This is used to confirm and optimize cannula location and position (VV and VA ECMO).

Transthoracic ultrasounds (particularly subcostal views) are often adequate for confirming guidewire location (correct vessel) and positioning cannula.

The presence of skilled operator in sufficient number allows continued visualization of the J-loop of the guidewire using echocardiography. Careful communication with the primary operator(s) can alert the team to inadvertent wire kinking or migration.

Parasternal/apical imaging and Doppler can be used to confirm the correct orientation of dual-lumen catheters (return jet directed across tricuspid valve).

The length of the wires and catheters used in ECMO means that a 2-person team technique is better used for percutaneous cannulation: the primary operator is in charge of sequential dilatation of the skin/subcutaneous tissue/vessel, while the second (and potentially more important operator) controls the guidewire at all times.

Excellent teamwork skills and clear, concise communication are paramount to safe, timely, and efficient percutaneous ECMO cannulation.

These technical and nontechnical skills are particularly important when the potentially stressful situations in which ECMO can be inserted are considered.

Cannulation in extreme conditions, without the use of imaging, can be attempted. New cannulae allow insertion without dilatation. These techniques increase substantially the risk and should only be used in exceptional circumstance.

37.3.3 Ultrasound Tips

Ultrasound can be invaluable during ECMO cannulation – optimizing access location choice, confirming vessel patency, and guiding the choice of cannula size.

We advocate sterile, real-time US cannulation to minimize short- and longer-term cannulation issues.

Femoral vessels should be imaged distal to the inguinal ligament.

Femoral veins: the femoral vein should be cannulated away from the insertion of the long saphenous vein to avoid shearing it away from the FV during serial dilatation and cannulation.

Femoral arteries: the femoral artery should be imaged in both the short and long axes. The radius of the vessel should be measured in the long axis to avoid overestimation of size and attempts at inserting excessively large arterial cannula.

The diameter of an ECMO catheter in mm is one-third of its size in French gauge (i.e., a 21 Fr catheter has an external diameter of 7 mm).

The catheter should be inserted into the common femoral artery, distal to the inguinal ligament but proximal to the bifurcation into the superficial femoral (SFA) and profunda femoris (PFA) arteries.

Inserting the cannula close to the bifurcation may complicate later surgical repair (after decannulation).

It is much easier to insert the “backflow” or reperfusion catheter guidewire anterograde down the common femoral artery prior to inserting the ECMO cannula retrograde into the distal aorta. It is possible to do it subsequent to the cannula insertion (in case of emergency) but will require skills and patience.

37.3.4 Peripheral VA: Backflow Cannula Insertion

The “backflow” or reperfusion cannula guidewire should be inserted into the common femoral artery, but the guidewire should be seen to be directed down the superficial femoral artery and not the profunda femoris artery.

In-plane real-time US can be used to guide this procedure.

The guidewire has a tendency to feed down the PFA due to the angle of insertion. This can be overcome by rotating the needle 180° just as the guidewire approaches the bifurcation.

37.3.5 Difficult Cannulation

Cannulation difficulties can arise for even the most experienced operators.

A two-person technique may alleviate frustration when difficulties are encountered.

Wherever possible, the Seldinger serial dilatation technique is preferable to a surgical approach in terms of minimizing longer-term bleeding complications. When an open surgical approach is required, it is preferable for this to occur in an operating theatre with the procedure performed by an experienced cardiovascular surgeon.

Dilators with a very long taper assist in dilatation of even the most difficult subcutaneous tissues.

When the subcutaneous dilators are advanced and meet resistance, we advocate rotation of the dilator such that a significant amount of torque is applied to the skin and subcutaneous tissue. With the torque maintained the dilator is withdrawn and the soft tissues tend to “give” around the dilator. The dilator is then readvanced.

At all times the operator should ensure free movement of the guidewire.

If a small surgical skin incision is required, a single insertion of the scalpel blade with the blunt end of the blade run along the guidewire may limit bleeding complications. Aggressive and multiple skin incisions are associated with increased bleeding rates at the cannulation site.

37.3.6 Kinking the Wire

The guidewire may kink during cannulation, and it is important to recognize this complication quickly to avoid extravascular insertion of a larger dilator or the cannula.

The guidewire should be withdrawn until the kink is external to the patient (while making sure not to completely withdraw the guidewire).

If the kink cannot be straightened (unfortunately common), it can often be exchanged by inserting a smaller dilator than the one that kinked the wire back into the vessel, removing the kinked wire and replacing it with a new one.

Spare guidewire kits are available and should always be available.

When performing multiple site cannulation, it might be possible to use the guidewire from the other cannula kit if one guidewire kinks.

The guidewire should not be discarded after the first cannula is in!

It is important to be aware of the length of the guidewire being inserted – a long multistage venous cannula cannot be used with a short arterial cannula guidewire.

The amount of guidewire external to the patient when using a longer guidewire for an arterial cannula must be kept in mind (problems with this can be overcome by real-time echo imaging of the J-loop).

37.3.7 Right Ventricular Perforation

Right ventricular perforation is a recognized complication of jugular cannulation – particularly when the Avalon cannula is being used as it needs to traverse the right atrium [10].

Multiple premature ventricular ectopic beats may indicate that the guidewire is in the right ventricle.

Tamponade is the near-inevitable result of perforation of the right ventricle. This can occur slowly (when the perforation is due to the wire) or very rapidly (when the perforation is with the cannula). If recognized and the cannula is the cause of the perforation, it should be clamped immediately but not removed.

The risks of this procedure can be decreased by employing the imaging techniques described above.

On the rare occasions it does occur, it is best managed with urgent surgical repair. Undertaking cannulation in the operating theater with a cardiothoracic surgeons performing the cannulation procedure or readily available increases the safety of the procedure but is not always possible.

Other vessels can be damaged, such as the inferior vena cava, coronary sinus, and hepatic veins [10, 11].

The interatrial septum may be perforated even by a femoral venous line inserted too far.

Some advocates the use of a long sheath to exchange the initial guidewire for a stiffer wire to minimize the risk of kinking with serial dilatation and cannula insertion. This prolongs cannulation time and increases its complexity.

37.3.8 Awake Cannulation

Patients requiring central ECMO and most patients requiring VV ECMO (after failure of conventional treatments for respiratory failure and de novo cannulation – e.g., in the hope of bridge to transplantation) are cannulated while anesthetized and ventilated.

There are a number of situations where patients may be cannulated awake.

This should be explained to them as much as practicable (and consent obtained).

A designated, experienced clinician or critical care physician should manage the patient's analgesia and hemodynamics during cannulation and be prepared for and capable of anesthetizing and managing safely the airways if the procedure is poorly tolerated or complications occur.

A generous amount of local anesthesia is required. Local anesthetic toxicity must be considered.

37.3.9 ECMO CPR

The decision to perform ECMO CPR should be considered early as there is a necessary lag time until support is established.

An ECMO CPR team and equipment should be readily available where this is being considered [12].

A pre-primed ECMO circuit will reduce the time to establish support [12, 13].

The primary resuscitation team should continue resuscitation in line with international guidelines. Interruptions to CPR should be kept to a minimum and therapeutic hypothermia should be considered [14, 15].

To facilitate cannulation of the vessel with the needle, passing the guidewire and minimizing sharp injuries, it is advisable to interrupt chest compressions until the wire has been fed into the vessel [16].

An automated cardiopulmonary resuscitation device may free additional personnel to focus on ECMO CPR and reduce fatigue from continued chest compression. It can cause occult intrathoracic or intra-abdominal organ damages that will cause subsequent problems. A team member will be required to manage/troubleshoot this device during the resuscitation.

Ultrasound should be used for cannulation, whenever possible.

During CPR it can be difficult to identify venous from arterial blood on aspiration. The venous blood may paradoxically appear more pulsatile during CPR.

Defibrillation safety is paramount, and defibrillation should be delayed until all operators are able to stand clear of the patient.

When ECMO has been established, definitive diagnosis and treatment of the underlying cause of arrest can be addressed.

37.4 Maintenance

37.4.1 Low-Flow Alarms

This is perhaps the most common alarm heard while patients are on ECMO. It must prompt an immediate search for possible causes.

It may simply identify that the alarm limit is set above the current flow rates (e.g., immediately after changing the pump settings). It is advised to set the alarm at 500 mL/min below the current or desired flow reading.

Cause of low-flow alarm includes:

- Access insufficiency. It is unusual, but not impossible, for circuit flows to be limited by return cannula size.
- Kinks or occlusion of the circuit tubing or cannula.
- Oxygenator thrombosis. This can be suggested by a rising transmembrane pressure gradient and falling ECMO flows. The oxygenator may have visible thrombus within it (but this can occur without obvious thrombus). Although the transmembrane pressure gradient will fall slightly when the pump speed is turned down, the flows will not improve.
- Systemic hypertension or vasoconstriction in patients on VA ECMO may cause low flow (an increased afterload to the pump). This is usually only seen to activate the alarm when the changes occur suddenly, for example, coughing/waking.
- Air embolus. Low-flow or “no-flow” alarms may be the first indication of an air embolus when the presence of gas bubbles prevents the ultrasonic flow probe from estimating flow. More dramatically, an air lock in the pump head will stop flow entirely. This complication is discussed in greater depth in Chap. 36.

37.4.2 Access Insufficiency

Access insufficiency or “suck down” occurs when the venous return to the access cannula(e) is insufficient for the degree of pump suction at the set pump speed [3].

In circuits with a negative pressure monitor on the access side, this will be suggested by the access pressures falling below -100 mmHg .

Where the access pressures are not measured, the first signs of may be variations in the flow, swinging of the access cannula, and subsequently “kicking” of the access line with activation of the low-flow alarms on the pump. This usually indicates a negative pressure much greater than -100 mmHg .

The excessively negative pump suction (relative to venous return) results in the vessel wall being sucked onto the access ports of the cannula and obstructing flow into the pump.

Swinging and kicking of the ECMO lines, the most obvious manifestations of access insufficiency, are rarely seen when using dual-lumen catheters.

Immediate interventions are to reduce the pump speed (to disengage the vessel wall from the access cannula) – paradoxically, the flows will tend to increase with this maneuver – and to correct any underlying volume disturbance.

Access insufficiency is a common problem when the access cannula is positioned too low (in the more collapsible extrathoracic inferior vena cava).

A careful examination of secondary causes for reduced venous return to the heart should be considered:

- Bleeding (both obvious and covert)
- Excessive diuresis
- Other forms of hypovolemia
- Coughing, straining, and increased intra-abdominal pressure

Access insufficiency can be suggestive of tamponade or tension pneumothorax, and these should be looked for with echocardiography/CXR/US if simple interventions fail to resolve the issues.

Where access insufficiency continues to be problematic, the patient still needs high flows (if not higher flows), and secondary causes have been eliminated; a second access cannula can resolve the issues and allow high-flow VV ECMO.

37.4.3 Recirculation (VV ECMO)

Recirculation can be identified when blood in the access cannula appears better oxygenated than the patient's saturations would suggest – that is, the blood being drawn into the ECMO circuit is oxygenated blood from the return cannula, not deoxygenated blood from the systemic venous system.

It can be confirmed by taking a preoxygenator blood gas. If the access and return cannulae are too close within the venous system, recirculation is more likely to occur and their position(s) should be adjusted.

Recirculation increases as flow increases and the system will become less efficient.

Recirculation occurs less often with dual-lumen catheters [1], and this often compensates the lower flow obtained with this cannula, in relation to the overall efficiency of a circuit.

37.4.4 Inadequate Support

37.4.4.1 VV ECMO: Persistent Hypoxemia

When a circuit can deliver 3–5 L of oxygenated blood to the right atrium but the patient's native cardiac output is significantly higher than this, they will remain hypoxic (although less hypoxic than in the absence of VV ECMO). This is effectively a shunt.

Options to improve tissue oxygen delivery matching include increasing the ECMO flow (reducing the size of the shunt), increasing the oxygen-carrying capacity of the blood (transfusion), and reducing systemic oxygen requirements (aggressive treatment of sepsis, preventing fever, consider active cooling, and even moderate therapeutic hypothermia).

This is analogous to the approaches to addressing inadequate tissue oxygenation in the non-ECMO patient.

Circuit flows can be increased by optimizing cannula(e) position and volume state or by introducing a second access cannula (e.g., high-flow VV ECMO).

37.4.4.2 VA ECMO: Vasoplegia

Patients can remain hypotensive even with VA ECMO flows of 4–6 L in the setting of vasoplegia.

When seemingly “adequate” ECMO flows have been established, vasoplegia should be managed aggressively with potent vasoconstriction.

Causes of vasoplegia should be looked for and treated (sepsis is most likely but other forms of high-output cardiac failure should be considered, as well as acute spinal cord injury).

37.4.4.3 Peripheral VA ECMO: Pulmonary Edema

This can occur in the setting of aortic valve regurgitation where the left ventricle gradually fills and dilates if the regurgitant volume exceeds the amount of blood ejected.

Echocardiography can confirm the diagnosis.

Suggested interventions include increasing PEEP, reducing the ECMO flows as permitted by systemic flow requirements, and increasing inotropy to assist left ventricular ejection.

If these interventions fail, then consideration should be given to proceeding to central VA ECMO, left ventricular assist device (LVAD), or biventricular assist device (BiVAD) insertion with aortic valve replacement/repair and/or a left ventricular vent.

An alternative cause for pulmonary edema on ECMO can be in the setting of isolated left ventricular failure and residual adequate right ventricular function.

All of the venous return not captured by the access cannula of the ECMO circuit is pumped by the right ventricle into the pulmonary circulation, and it is not able to be ejected by the failing left ventricle.

Suggested interventions include increasing the ECMO flows, increasing the PEEP, and reducing inotropy (any exogenous inotropes are most likely to further augment RV function and accelerate the pulmonary edema).

These interventions should be carefully monitored with echo and reassessment.

If the patient remains in pulmonary edema and hypoxic, then a high-flow VA ECMO configuration with a second venous access cannula can be considered.

37.4.4.4 Peripheral VA ECMO: Differential Hypoxia

Differential hypoxia occurs when the native cardiac function returns but the patient has hypoxic respiratory failure.

The deoxygenated blood that reaches the left ventricle via the pulmonary circulation is ejected into the ascending aorta, and the patient’s native cardiac output supplies the first branches of the aorta (the coronary arteries, the brachiocephalic trunk, and the left common carotid artery).

This can lead to myocardial and cerebral ischemia with potentially fatal consequences.

Suggested interventions include early diagnosis and management of the primary cause of the respiratory failure (particularly if it relates to pulmonary edema and identifying the mechanism of the pulmonary edema) and temporarily attempting to

reduce the output of the left ventricle to prevent hypoxicemic injury to the myocardium and brain:

- Increasing ECMO flows (and considering conversion to high-flow VA ECMO configuration)
- Reducing exogenous inotropes
- Considering simultaneous VV and VA ECMO (VVA ECMO) or, where myocardial recovery is sufficient, conversion from VA to VV ECMO
- Considering conversion to central VA ECMO or peripheral VA ECMO with the return cannula moved to be a side graft onto the axillary or subclavian artery [4]

37.5 Cardiac Arrest on ECMO

37.5.1 VV ECMO

Patients who arrest on VV ECMO need CPR as per standard protocols with careful attention to securing the cannula(e) [14, 15]. Defibrillation should occur as per published guidelines.

If the cause of the cardiac arrest is hypoxemia and the patient had previously been well supported on VV ECMO, then the circuit should be interrogated for potential issues – confirm power supply, oxygen supply connected to the oxygenator, ensure FiO_2 is at 1.0, and sweep gas at least equal to blood flow rates.

Consider a fluid bolus and blood transfusion to improve ECMO flows and tissue oxygen delivery.

Alternative ECMO-related causes of cardiac arrest include hemorrhage and air embolus (see Chap. 36).

37.5.2 VA ECMO

Cardiac arrest on VA ECMO is often not hemodynamically significant – certainly if the patient has very little native cardiac function at the time of the arrest.

In some cases, the arrest may only be recognized by dysrhythmia on the monitors (e.g., asystole or ventricular fibrillation), when there is loss of pulsatility in a previously pulsatile patient (if there is not an IABP in situ), or when the triggering on the IABP becomes irregular.

It is not necessary to perform CPR immediately in a patient who suffers a cardiac arrest on VA ECMO as the circuit (as long as it is functioning) will sustain cardiac output.

Look for and treat reversible causes (patient and circuit).

In a patient who was only partially dependent on ECMO, increase the ECMO flows as tolerated by the circuit.

In the setting of ventricular fibrillation/ventricular tachycardia, it is advisable to defibrillate, as prolonged dysrhythmia will have significant implications for

weaning from ECMO when this is suitable and ventricular distension can lead to cardiac ischemia.

Blood stasis in the cardiac chambers might lead to clot formation and increase the risk of stroke or peripheral embolization if pulsatility returns.

ECMO-related causes again include pump failure, oxygenator failure, hemorrhage, and air embolus.

37.6 Awake ECMO and Mobilizing the ECMO Patient

Awake ECMO is now possible and has been described for both peripheral VA and VV ECMO [7, 17–19].

Benefits include prevention of deconditioning, pressure areas, and other side effects from prolonged sedation in the ICU. It decreases the occurrence of delirium and the need for high doses of sedatives. Patient can exercise and enjoy the presence of their families. We routinely provide a game console for such patients.

Potential risks are those from cannula(e) dislodgement with excessive movement making the awake patient more difficult to manage.

Patients who are awake and on ECMO for extended periods of time may become depressed.

Careful patient selection, explanation and reinforcement of the need for cooperation with the treating team from the outset, as well as clear and explicit plans for future management may help to alleviate problems.

Mobilizing ECMO patients should be undertaken with appropriate staffing levels and equipment available.

Securing the cannula during mobilization can be difficult, and many institutions have developed their own systems [4, 19].

At our own institution, mobilization is undertaken in the presence of a dedicated ECMO specialist and at least one additional ECMO-trained staff member specifically managing the cannula(e) and lines, in addition to those team members required to mobilize a non-ECMO ICU patient.

Difficulties arise when no solution to the medical condition having triggered the use of ECMO is found. The patient can then take part in end-of-life decisions and planning.

37.7 Miscellaneous Laboratory Issues

37.7.1 Unable to Anticoagulate

Some patients demonstrate relative heparin resistance while on ECMO, and it can be difficult to achieve preset anticoagulation targets.

Investigations should include confirming that heparin is being administered, checking clotting factor, anti-Xa and anti-thrombin (AT) levels, and careful liaison with a consultant hematologist.

Consideration may need to be given to antithrombin replacement where patients are found to be deficient.

Coagulation issues are complex and still poorly understood.

37.7.2 Fever and Elevated White Cell Count

Infection is a common complication in patients treated with ECMO.

Prolonged duration of ECMO support is consistently associated with an increased risk of nosocomial infectious complications [20–24].

The role of prophylactic antimicrobial therapy in patients on ECMO is controversial and varies between institutions.

Patients should not receive antimicrobials therapy simply because they are supported by ECMO.

Infection can be difficult to diagnose in the patient on ECMO:

- Fever may be masked by the extracorporeal circuit.
- A systemic inflammatory response may occur in the setting of extracorporeal life support, in the post-cardiac surgical patient, and in the face of massive transfusion.
- The use of steroids as part of the treatment for respiratory and/or cardiovascular failure may be associated with leukocytosis.
- The patient may have required ECMO for support of sepsis (respiratory or systemic), and secondary infection may be difficult to distinguish from progression of underlying disease.
- Sepsis, severe sepsis, and septic shock may occur in the absence of an elevated white cell count, particularly in the immunosuppressed patient.

There are no standard diagnostic criteria for infection occurring on ECMO.

New onset of pressor dependence may be the only indication of secondary infection in some circumstances.

In the setting of rising temperature and white cell count, a thorough search for infection must be undertaken and appropriate cultures sent.

Where possible, lines should be changed and empiric antimicrobial treatment instituted based on likely source of infection, local antibiograms, and patient allergies.

Empiric antifungal treatment should be considered as *Candida* spp. are consistently identified as a leading cause of infection in adult patients on ECMO [20, 21, 23].

The kinetics of antimicrobial therapies during ECMO is under ongoing investigation.

Where possible, drug levels should be monitored.

It is not feasible to change the ECMO cannula(e) on the suspicion of infection.

However, when it is clear that the cannula site is the cause of infection (e.g., abscess at cannulation site), changing the cannulation strategy should be considered.

Where this involves VV ECMO, consideration should be given to changing from femoro-femoral cannulation to dual-lumen jugular cannulation or vice versa.

37.7.3 Thrombocytopenia

Thrombocytopenia is common in patients on ECMO.

Transfusion thresholds vary between institutions and will vary according to the type of ECMO and initial disease process.

In bleeding patients, the platelet count should be maintained in the normal range ($>50-100 \times 10^9/\text{L}$) [19, 24].

Where thrombocytopenia is thought to be due to heparin-induced thrombocytopenia (HIT), heparin should be stopped immediately, HIT-screen sent according to institutional protocols, and alternative anticoagulation therapy instituted. Heparin-coated circuit should be changed to non-coated ones. Argatroban and bivalirudin have been used successfully [25, 26].

37.7.4 Increased Plasma-Free Hemoglobin

Plasma-free hemoglobin (plasma-free Hb) can be monitored as a measure of hemolysis.

Potential ECMO-related causes of increased plasma-free hemoglobin can include thrombus within the extracorporeal circuit, excessive suction from the centrifugal pump (potentially generating subtle access insufficiency and red cell trauma), and overt access insufficiency.

The plasma-free hemoglobin can be elevated by damage to the red cells during sampling so a single isolated result should be repeated with careful attention to how the sample is measured.

When the plasma-free hemoglobin is consistently elevated, a comprehensive assessment of the circuit and cannula, pump speed, and anticoagulation strategy should be undertaken and consideration given to changing the circuit [19].

37.8 The X-Ray

37.8.1 Cannula(e) Position

X-ray can monitor ECMO cannulae position.

The type of cannula in situ will affect the interpretation of the X-ray.

The clear plastic access ports at the tip of many single-lumen cannulae currently available are radiolucent. The catheter is more proximal than would be suggested by the appearance of the radiopaque reinforced area on X-ray. An exception is the multiple-stage access cannula where the reinforced area extends all the way to the tip of the cannula.

Ultrasound and echocardiography can visualize the tips of the cannula regardless of the material.

It is important to monitor the cannula position regularly to avoid the potentially disastrous complication of accidental decannulation.

Small movements in cannula position may limit the efficacy of the ECMO support (e.g., recirculation).

Clinical monitoring of the cannula position can include nursing-led checks of measurements of cannula landmarks from skin entry.

37.8.2 Pneumothorax Management

Despite ventilatory strategies aimed at minimizing barotrauma and ventilator-induced lung injury, pneumothoraxes are relatively common in patients on ECMO.

Intercostal drain insertion is often associated with a much greater risk of bleeding in patients on ECMO. Thoracotomy can be performed in these situations but substantially increase the overall morbidity and mortality.

The ELSO guidelines recommend a conservative approach to pneumothorax management in ECMO patients:

- A small pneumothorax (estimated 50 % or less with no hemodynamic compromise and no enlargement over time) is best managed by waiting for absorption with no specific treatment.
- A symptomatic pneumothorax (>50 %, enlarging, or causing hemodynamic compromise) should be treated by external drainage.

There are occasions when we would advocate draining a relatively asymptomatic pneumothorax (e.g., patient almost weaned from ECMO in the hope that re-expansion may facilitate weaning).

Any procedure undertaken on a patient on ECMO should be performed by an experienced operator and with the coagulation profile optimized.

Consideration should be given to stopping systemic heparin, ensuring platelet count is high enough and the use of antifibrinolytics such as tranexamic acid.

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Part VII

Transport of the ECMO Patient

Antonio F. Arcadipane and Gennaro Martucci

38.1 Introduction

Extracorporeal life support (ECLS) for cardiopulmonary or respiratory failure is one of the most specialized medical and technological activities and is available only in experienced centers. Without mobile support, it might be impossible to transport patients needing extracorporeal membrane oxygenation (ECMO), and transportation of a patient requiring ECMO is often unavoidable if that patient requires prolonged treatment in a referral center [1].

The increasing cooperation between medical institutions and specialists, broader indications for ECLS, and progressive miniaturization of ECLS equipment, as well as the increasing recognition that high volume centers achieve better outcomes, are likely to increase the need for patient transfer in the near future [2].

Aeromedical transport is used to transfer critically ill patients over large distances or in areas with inadequate road networks or geographical and infrastructural barriers. It comprises fixed-wing aircraft and rotary-wing aircraft (helicopter). By definition, ECMO transport is principally a secondary transport: from a referring hospital to a referral hospital for specialized treatment.

The goal when transporting critically ill patients is to continue current ICU treatment as safely as possible throughout the journey and to be in a position to provide additional emergency treatment if necessary. This goal must be achieved in the minimal and unfriendly space of aircrafts, helicopters, and ambulances. So, in a sense, ECMO transport teams are a mobile extension of ECMO centers.

In this chapter we will address some general concepts and practical aspects to prepare and conduct a safe ECMO transport, beginning with some history, and

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address basic concepts of physiology and crew resource management that are fundamental for all kinds of transport, and even more so in the complex experience of an in-flight ECMO patient referral.

38.2 History of Interhospital Aeromedical Transport

Aeromedical transport grew out of basic military models into integrated civilian systems of care [3]. Airplanes began transporting casualties during World War I when Serbian patients were carried in an unmodified French fighter plane. In 1916, Dr. Eugene Chassaing suggested to the French government that it modify an aircraft to allow it to carry two stretchers. The first documented case of helicopter transport of an injured patient was in Burma during World War II, on April 23, 1944, and the first dedicated use of helicopters by US forces occurred during the Korean War, between 1950 and 1953.

The Vietnam War was the definitive showcase for demonstrating the efficacy of helicopter medical rescue transport: over 400,000 patients were airlifted to hospitals during this conflict.

Expertise in the use of air ambulances evolved in parallel with the evolution of aircraft design. The use of military aircraft as battlefield ambulances continues to grow and develop today in a number of countries (e.g., UH-60 Black Hawk helicopters recently employed by US military during the Iraq War).

From their use in the military, air ambulances were introduced into the civilian environment, where they are now used for primary scene retrieval and secondary inter-facility transport in modern health systems.

The initial civilian uses of aircraft as ambulances were probably incidental. In northern Canada, Australia, and in Scandinavian countries, remote, sparsely populated settlements are often inaccessible by road for months. So air ambulances quickly established their usefulness in remote locations, while their role in developed areas increased more slowly.

In Los Angeles in 1947, J. Walter Schaefer founded the first air ambulance service in the United States.

The first permanent civil air ambulance helicopter was the Christoph 1, at the Harlaching Hospital in Munich, Germany, in 1970. The success of this initiative led to a quick expansion of the concept across Germany to roughly 80 helicopters at present.

The US Air Force began ECMO transport in late 1985 [4], and in 1994 Critical Care Air Transport Teams (CCATs) were implemented as an extension of the ICU resuscitation phase of combat casualty care. In 2005, emerging need for specialized treatment of ARDS led to the creation of the Acute Lung Injury Response Team (ALIRT) [5, 6].

In the last few years, a number of international centers have reported increased experience in interhospital ECMO transport [7, 8].

There are a variety of helicopters used for civilian health emergency medical systems (HEMS). The most commonly used types are the Bell 206, 407, and 412;

Eurocopter AS350, BK117, EC130, EC135, and EC145; Sykorsky S76; and the AgustaWestland 109 and 139. These aircraft are normally configured to transport one patient and three to five medical personnel, but some can be configured to transport two patients if necessary.

In our ECMO program, at ISMETT, we currently employ an AgustaWestland 139, which can carry one patient, everything needed for ECMO function (Fig. 38.1), and our ECMO team [9], composed of an anesthesiologist, a perfusionist, and either a cardiac or thoracic surgeon. In addition, there is room for two other people (e.g., fellow and nurse) (Fig. 38.2).

Many aircraft have been used for medical transport: small executive jets or turboprops, though listing of all of them would be beyond the purpose of this chapter.

The Lockheed C-130 Hercules, a military cargo plane, may be considered the best choice because it allows direct transport of an ambulance, without need for the loading and unloading of the patient or stretcher, and care is provided in the ambulance

Fig. 38.1 ISMETT setup for control unit and oxygenator pump unit (Maquet Rotaflow with PLS circuit) fixed by a certified plate on the helicopter floor



Fig. 38.2 Agusta Westland 139 cabine view



environment. On the other hand, this poses several organizational concerns. Because it is a military means of transport, there needs to be close collaboration between the national Air Force and the medical system. It is also time-consuming because the C-130 has to reach the airport nearest to the hospital, and one has to also consider the distance from the landing area to the referral center. Finally, C-130 transport imposes extremely high costs, which are affordable only in select conditions.

38.3 How to Choose the Right Means for the ECMO Patient

The use of air medical transport in Europe, the United States, and Australia differs dramatically and is influenced by distances between hospitals, the history and development of medical services, cooperation with the military, geography, and insurance policies.

The principal advantage of air transport is the shorter journey time, and it is generally considered one of the preferred modes of secondary transfer [10, 11]. Air transport should be considered for journeys longer than approximately 80 km, though the velocity of the craft needs to be adjusted for potential organizational delays and the need for transfer between vehicles. A useful benchmark would be to use air transport when it would save at least roughly 2 h compared with ground transport.

Fixed-wing flights constitute a significant portion of aeromedical transport and are preferred when distances are more than 350–400 km, with the considerable advantage of being able to travel in inclement weather. The biggest disadvantages of conventional aircrafts are that they require airports to collect and deliver their human cargo and hospitals are rarely near airports, so this inevitably requires ground transfers. Takeoff and landing times should also be taken into account.

Medium range aircraft provide adequate working space for patient care and can fly within a range of 500–1,500 km and reach speeds of up to 250 knots. Small jets have the longest range, up to 5,000 km, and the fastest speed (up to 450 knots). However, their streamlined shape severely limits cabin space, interfering with the care for the critically ill patient.

Helicopters typically cruise at 120–150 knots (220–280 km/h), with a useful radius of 50–400 km. The advantage over fixed-wing aircraft is the ability to operate from a range of surfaces, and helipads are more diffuse than airports [12]. The maximum advantage is found in areas with underdeveloped roadway systems [13].

As demonstrated during the H1N1 pandemic, delivery of advanced medical technology can be achieved even in remote and underserved areas that present a variety of geographical barriers. Adoption of an appropriate means of transportation [14] and use of a multidisciplinary team are the key elements for the success of the ECMO rescue mission and improve the chances that critically ill patients will not only arrive safely at the referral hospital, but will also be discharged well enough to enjoy the trip home [15, 16].

The choice between rotary-wing aircraft (helicopters) or fixed-wing aircraft should be made following a cost versus benefit analysis, using criteria such as travel distance, landing infrastructure, weather conditions, and clinical emergency.

38.3.1 Preparing for the Transport

Principles for avoiding critical events during transport are based on extensive anticipation, effective communication, and patient assessment/stabilization [17]. Though stabilizing the patient before transport is mandatory, it can be time-consuming, so the degree of stabilization should be dictated by the estimated time of arrival at the referral hospital [18].

It is not redundant to say that transferring a patient on ECMO support from one facility to another should not be viewed as an extraordinary event, but as an integral part of an ECMO transportation program.

Before transport, all therapeutic options have to be explored with the referring hospital. In some cases an ECMO team from the referral center could be sent to personally evaluate the patient and determine the requirements for transport. The transport then involves a complex interplay between the referring hospital, the transport team, and the receiving ECMO Center.

In general, early referral is preferred so that the ECMO center can apply rescue therapies not yet considered impossible in that context before ECMO support starts.

During initial communication between the hospitals, the ECMO team leader must confirm the availability, at the referring hospital, of some required equipment and supplies: 2–4 units of packed red blood cells, an echography machine, a large sterile surgical drape to completely cover the patient, and a small surgical light for possible surgical isolation of vessels in case of impossible percutaneous cannulation. These requests are part of our protocol of ECMO placement. As far as requesting blood products, some centers ask for a large quantity of packed red blood cells to be available, while our protocol calls for only a safely adequate supply because we operate in an area with a limited availability of blood.

Before starting operations at the referring center, the transport team should always meet with the patient's family to describe the nature of the support and the type of transport.

38.3.2 Equipment

ECMO devices have become increasingly smaller thanks to centrifugal pump-based systems, shorter circuits, and miniaturized monitors [19]. It is important to bring a limited set of disposables instead of storing all possible items in a bulky emergency kit. Take into account that if stabilization prior to transfer is adequate, this equipment is seldom used. The kit should be inspected prior to each departure. Clear labeling increases awareness of the site of the material and avoids time-consuming searches.

The number of oxygen cylinders to be transported depends on the duration of transfer and the size/capacity of the cylinders. Ensure that all cylinders are full before transport. Hoses and adapters must be compatible with those of the facility, ambulance, and aircraft. The monitor has to be compatible with all equipment available or in use (e.g., saturation cable and arterial pressure transducer connection cable).

All the ECMO equipment must be certified by the national or international flight safety agency, or the pilot will not allow you to bring it onboard. The use of a dedicated checklist just before departure is part of a systematic safety check of equipment and drugs.

38.3.3 Before Departure

Stabilization of the ECMO patient involves optimization of DO₂, though hemodynamics should be carefully assessed.

The ECMO circuit right function has to be tested, and whenever a doubt arises, a chest x-ray should be done to check the cannulae position and possible need for repositioning. Any necessary intervention and/or pharmacologic treatment needs to be done prior to leaving the referring hospital [20, 21].

All IV access, infusion lines, monitoring equipment, and drains must be checked, rechecked, and secured. Spare IV access is mandatory, and all unnecessary medication must be discontinued before the transfer. Particular attention must be given to monitoring the ECMO cannulae positions and to preventing any kinking within the ECMO circuit, along with a careful connection of the membrane lung to the oxygen supply.

38.3.3.1 What to Check

- Whether there are enough spare syringes to cover the patient's needs during transport
- Which medications are indispensable and which can be interrupted temporarily
- Whether there is special and adequate tubing, depending on the type of pump
- Battery power and the number of wall sockets available

Preparation of medications and syringe pumps will be easier in the secure environment of an ICU than in the close confines of a shaky helicopter or a small aircraft, with possibly poor lighting. In many helicopters, and certainly in small airplanes, the ceiling is not high enough to guarantee a sufficient spontaneous flow (because of gravity) of IV fluids. Therefore, pressure bags or additional infusion pumps may be needed. Glass bottles should be avoided. Beware of air embolism from pressurized intravenous lines.

A so-called time out for the transport team before departure is now successfully being used as a security check. Items on a checklist should include the following:

- Patient's name and diagnosis.
- Comprehensive documentation, including radiography and laboratory exams: the patient's medical chart is a legal obligation and an integral part of patient care.
- Destination unit, shortest route from the landing pad/ambulance point of departure.
- Final check of weather conditions.
- Name and phone numbers of physician responsible for the transfer.
- Duration of the transfer and subsequent calculation of required quantities of medical gases, medications, and other equipment.
- Possible Plan B for transfer.

38.3.4 During Transport

In helicopters, internal noise levels are frequently >95 dB, so that normal conversation is impossible. Auscultation is impracticable, as is reliance on audible monitor alarms. Earplugs have to be used for all patients, regardless of conscious state, to prevent hearing damage. Cabin lighting may be poor because strong lighting can distract the aircrew and adversely affect pilot night vision. All this may make monitors, cyanosis, veins, and patient movement difficult to see. Vibration is greatest at takeoff and landing and may induce pain in unstable fractures; it also makes accurate adjustment of fluid infusion rates difficult [18].

Often fixed-wing aircraft suffer from less noise but are characterized by stronger acceleration/deceleration forces during landing/takeoff.

Incidents related to transport are mainly associated with equipment-related problems, vascular line management, inadequate monitoring, and inadequate communication among staffs.

38.3.4.1 What to Monitor

- Three-lead (or more) ECG with heart rhythm and ST segment monitoring.
- Invasive pressures (if too time-consuming or not available, noninvasive blood pressure is acceptable in case of emergency cannulation in life-threatening conditions; but before transport the patient should be fully monitored, and it is worthwhile to wait for invasive arterial pressure monitoring).
- Hemoglobin oxygen saturation. For long-term transport, SvO_2 is mandatory either by full optioned Cardiohelp System (Maquet) or portable point of care ABG machine.
- End-tidal capnography, if available.
- Temperature: airplanes that reach higher altitudes have greater temperature drops, with risk of hypothermia for a critically ill patient.

Complete assessment of the patient and equipment is mandatory throughout the transport. In addition, there are some particularly crucial things to consider:

- Patient movement to and from the transport vehicle, including to/from the stretchers and helicopter
- Securing of the patient, the circuit, and oxygen supply during takeoff and landing
- Effects of altitude on membrane gas exchanges
- Recognition and management of in-transport emergencies

38.3.4.2 Effects of Altitude

With an increase in altitude, temperature and barometric pressure decrease, and the partial pressure of oxygen drops. This effect also influences the gas exchange capacity of the membrane.

Furthermore, according to Boyle's Law, as the atmospheric pressure falls, gas volume increases. At a typical helicopter altitude of 2,000 ft, this increase is about 8 %. In the case of fixed-wing transport, the problem is less essential but still present. Pneumothoraces, pneumoencephaly, bubble emboli, and air trapped in the abdominal cavity will all expand in proportion to the drop in cabin pressure. All surgical drains should be unclamped and patent. Air in the endotracheal cuff also expands, with possible tracheal injury. ETT cuffs should be filled with saline [22] or

have their pressure rigorously checked and adjusted in-flight. Pulmonary artery catheter balloons should be fully deflated.

These are just some of the considerations that dictate complete stabilization and assessment of the potential ECMO patient before transport, though this should be done for all transported patients.

38.3.4.3 Acceleration/Deceleration Forces

When a supine patient is exposed to the force of sustained acceleration or deceleration in the longitudinal plane, blood flow is diverted to either the feet or the head depending on the patient's orientation. Theoretically, this blood flow diversion can cause cerebral underperfusion or excess perfusion (if the force exceeds cerebral autoregulation), with a risk of deterioration in patients with an intracranial pathology. Cardiac preload and afterload can also be influenced by such forces, which can cause further deterioration in hemodynamically compromised patients.

The main problem, in any event, is related to circuit problems. During air transport the circuit and patient must be well secured to the aircraft and watched carefully during takeoff and landing to avoid shifting in the position of the cannula or kinking and accidental dislodgment of the circuit. Movement of the patient is recognized as one of the more dangerous practices in critical care.

A safety procedure in an unfriendly environment is to always check all the monitored parameters without losing any of them during loading from one means of transport to another.

Prevention of hypothermia, or restoration of normothermia, must be ensured in all patients through the use of the so-called space blankets, electrical blankets, and/or infusion warming systems.

38.3.4.4 Safety

Safety of the patient and aeromedical team is paramount. Staff should undergo training in aeromedical transport. For interhospital helicopter transport, additional training is required so the physician can adequately provide critical care support outside the ICU.

No pressure must be put on the aircrew to alter their normal safety procedures. The captain has the final say on whether the conditions are suitable for flight, independent of the patient's condition. On the other hand, a patient who has just been put on ECMO is usually stable enough to wait until easier and safer transport can be carried out.

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39.1 Introduction

Interhospital transportation of severe critically ill adult/paediatric patients is a high-risk procedure due to unstable clinical condition, lack of diagnostic/therapeutic tools, progression of the severity of disease and the consequences related to the equipment malfunction. These patients often require technology, staff and supplies that outweigh local resources and need to be centralized to regional tertiary care centres. The decision to set up transportation of such patients needs careful evaluation of risks and benefits [1–3].

ECMO instituted at referral centres allows stabilization of an unstable patient, otherwise unmovable, and thus a safer transportation to the targeted destination. Nevertheless, adding an ECMO system makes transportation more complex, requiring a specialized multidisciplinary ECMO team, trained and equipped to stabilize patients at the referring hospital, to apply and manage ECMO and to assist patients during transportation up to the tertiary care facility. Several large ECMO ground transportation international case series have been published in recent years, both for adult and paediatric patients [3–15]. Finally this method proved to be of utmost importance during the recent virus AH1N1 pandemic flu outbreak in Italy [16].

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Table 39.1 ECMO patient ground (ambulance) transportation: characteristics

Advantages	Disadvantages
Not influenced by weather	Shorter maximum distance coverage
Available night and day	Safety of transportation negatively affected by street roughness, other vehicles, traffic
Airports/heliport and secondary transportation not required	Slower
No need for a flight-trained medical emergency team	
More units available at the same time	

Ambulance ground transportation presents specific issues which will be addressed in this chapter. For a comprehensive analysis of air transportation issues, we remand to specific chapters.

39.2 Ground vs Air Transportation

When planning the logistics of transport, the choice of the means of transport is the first decision to take – several factors must be taken into account when considering the use ambulance instead of fixed wing/helicopter air transportation:

1. Distance from referral to tertiary care institution: the average distance covered varies among centres, often being on average less than 100 km. Nevertheless, patients have been safely moved up to 300–500 km ground distance [5, 8, 13].
2. Air or ground trained crew availability.
3. Geographical obstacles and/or availability of adequate roads.
4. Local resource availability.
5. Specific patient issues contraindicating air transportation.
6. Weather conditions [6, 7, 15].

The ambulance transportation advantages/disadvantages are summarized in Table 39.1. The vehicle employed is a mobile ICU unit, often customized to be used for this type of transportation and equipped with an ICU ventilator and an adequate monitoring system. Ambulance is adapted to provide extra space with enlarged power, oxygen and fuel supplies. Ambulance special technical requirements are summarized in Table 39.2. When the patient is moved by air transportation, ambulance is needed to cover short distances between the airport/heliport and the targeted hospital; alternatively ambulance can be loaded on large fixed-wing aircraft avoiding the time-consuming and risky procedure of on-/offloading the patient [6].

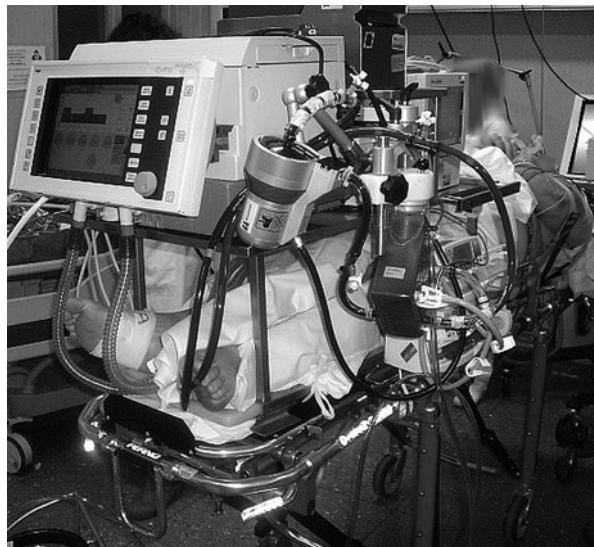
39.3 Equipment

Custom-made mobile steel carts or cradles have been developed by each ECMO centre to easily load all the equipment on the patient and to allow safe loading/unloading on the ambulance. Our custom-made steel cart (Fig. 39.1) extends in

Table 39.2 ECMO transportation ambulance technical requirements

Requirement	Reason
Adequate space (enlarged)	
Reinforced ambulance stretcher and stretcher holders	To support increased weight (ECMO pump, ECMO heater, ICU ventilator)
Reinforced shock adsorbers	To mitigate the effect of street roughness on the devices employed (especially ECMO pump)
Increased compressed oxygen storage	To support both ventilator MV and ECMO oxygenator sweep gas at iFO_2 100 %
Increased battery capacity	To support air heater/cooler, ICU ventilator, ICU monitor, infusional pumps, ECMO pump, ECMO heater
Increased fuel tanks	To avoid the need for fuel supplying during transportation

Fig. 39.1 ECMO transportation custom-made steel cart at the end of patient preparation. Special attention should be paid to weight distribution on the stretcher



height (100 cm) and provides two supports on two levels. It mounts on the spinal board over the patient's feet and allows transportation of the ECMO unit (driving pump, heater and console), an ICU ventilator and an ICU monitor. Moreover, a especially designed iron post allows holding of infusional pumps, pressure bags and fluids. A power strip is fixed on a post to organize electrical cables. Patient-cart unit is then secured and loaded on ambulance stretcher (maximum tolerance 250 kg). When loaded on the ambulance (Fig. 39.2), it may be secured with additional ropes to avoid rolling of the patient-cart unit and displacement of the equipment.

All the equipment needed for cannulation, priming of ECMO circuit and emergency procedures are listed in checklists and organized into backpacks. Backpacks and electrical equipment must be checked before departure, and materials must be replaced immediately after use.

Fig. 39.2 Patient-cart unit loaded on the special ICU unit and secured. Of note, up to three ECMO team members can sit on the right of the patient during transport (ECMO pump, ventilator and monitoring), while other two members can sit at the head of the patient (drug infusions and artificial airway management)



39.4 Pre-transport Preparation

On arrival the ECMO team gets clinical informations from the referring medical staff and takes charge of the patient. It's important to avoid unnecessary delays of referral; the ECMO team will attempt to get the most stable clinical condition after ECMO is started and the patient is positioned supine on the stretcher. The cart will be placed on the stretcher and carefully loaded with special attention to weight-balance the

cart. All the equipment will be checked again while on battery energy supply and tightly secured. Only after these procedures the patient will be moved to the ambulance. Moving the patient to the ambulance, oxygen to both the ECMO membrane lung and the ventilator will be provided by at least two small oxygen tanks. Power and gas supplies will be replaced by ambulance power inverter and gas tanks once loaded.

39.5 Team

The ECMO team is multidisciplinary and should be staffed by experienced and trained personnel. The team must be able to apply and run ECMO via peripheral venous-venous or venous-arterial cannulation and to front serious adverse events (see below). The number and composition of the group may vary from a minimum of three [5, 17] up to 15 [7, 10, 18], depending on the distance of the referring hospital (i.e. need for two drivers, support vehicles) and the presence of trainees, logistics and local practices. More frequently, the team includes at least a perfusionist to provide ECMO circuit set-up and management, two ECMO skilled physicians (surgeons and/or critical care physicians or both), one or two critical care nurses and drivers. Although Seldinger cannulation technique is preferable, many groups include a cardiac surgeon in order to provide, when needed, direct vascular cutdown or rescue thoracotomy.

39.6 Adverse Events

The main reported adverse events may be grouped into equipment/vehicle-related technical failure or patient-related complications. To our knowledge no fatal adverse events have been reported during ground ECMO patient transportation. In 2002 Foley et al. [7] reported an incidence rate of minor adverse events of 17 % during 100 ECMO transportation (80 % ground transportation). The most frequent problem reported is due to acute loss of power supply due to battery or vehicle power supply failure [8, 10, 17, 18], even in the presence of back-up battery pack [7]. Other frequent complications are ML damage [5, 7], circuit tubing leakage [7] and pump/circuit uncoupling. Linden et al. [6] reported also a failure of an ambulance shock adsorber. Inadvertent ECMO cannula removal/dislocation is certainly the most feared accident, but, to our knowledge, it has never been reported in out-of-hospital setting. Also tracheal tube, IV lines and thoracic/abdominal drainages may be dislodged, requiring a stopover and dangerous emergency manoeuvres. Additional length of the ECMO circuit may be of help in positioning the patient. Correct management necessitate experience in transport medicine and careful patient/equipment loading/unloading, manipulation and handling [3].

Technological improvements in monitoring, ventilators and ECMO (lighter, shock/vibration-proof transportation centrifugal pumps, improved capacity battery packs) may provide safer transportation of these patients.

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Part VIII

Conclusion

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Extracorporeal gas exchange was first developed in the 1940s to replace heart and lung function in the context of cardiac surgery. Ever since, a great technical development occurred allowing a widespread use of this technique as cardiac and respiratory support therapy. In this chapter we will present some possible future perspectives of extracorporeal gas exchange. Technical aspects regarding materials and coatings of extracorporeal circuits will not be discussed in detail.

Since the 1970s Kolobow and Gattinoni have conceptually separated the function of gas exchange of the lung into oxygenation and CO₂ removal [1]. The same physiology also applies to extracorporeal gas exchange: blood passing through the membrane lung directly absorbs oxygen and hemoglobin is rapidly saturated; hence, oxygenation requires only a small oxygen flow, whereas to completely substitute the patient lung function, a conspicuous blood flow is needed. Oxygenated blood contains 150–200 ml of oxygen per liter; if venous blood is 70 % saturated, an ECMO system can approximately transfer 40–60 ml of oxygen per liter of blood flow. On the contrary, CO₂ removal requires a substantial gas flow in order to maintain the maximum blood/air CO₂ gradient to quickly transfer CO₂ from the extracorporeal blood into the open air. Since a great amount of CO₂ is available (550–600 ml of CO₂ per liter of blood, most as bicarbonate ions) in a small volume of blood, even a relatively low blood flow is adequate. For these reasons a high extracorporeal blood flow is mandatory for a hypoxic patient, whereas a low-flow extracorporeal system perfectly suits hypercapnic patients.

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Technological development of extracorporeal systems addressed both the high-flow systems (venoarterial or venovenous extracorporeal systems for refractory hypoxia) and the less invasive low-flow systems.

40.1 Extracorporeal Oxygenation and Future Perspectives

The amount of oxygen transferred through a membrane lung (VO_2ML) is described by the following equation:

$$VO_2ML = BF * (C_{OUT}O_2 - C_{IN}O_2)$$

where BF is expressed as liters per minute, $C_{OUT}O_2$ is the oxygen content (ml O₂ per liter of blood) in the reinfusion limb of the circuit, and $C_{IN}O_2$ is the oxygen content of the blood before entering the membrane lung.

BF: The main determinant of VO_2ML is the blood flow (BF); in the absence of $C_{IN}O_2$ variations (i.e., oxygenated blood recirculation or increase in venous oxygen content), the VO_2ML is proportional to the extracorporeal blood flow. Therefore, the choice of the size of the cannulae should be carefully evaluated to match the patient needs (degree of hypoxia, cardiac output, total O₂ consumption, etc.).

$C_{OUT}O_2$: The performance of modern membrane lungs is nearly optimal: blood in the reinfusion limb of the circuit is fully saturated, and when high FiO₂ is used, the oxygen partial pressure ($P_{out}O_2$) reaches very high values (500–600 mmHg).

By increasing the FiO₂ at the membrane lung, we often obtain a negligible increase of hemoglobin saturation; on the contrary the substantial rise of $P_{out}O_2$ determines a significant increase of the fraction of the oxygen found in the dissolved form: an increase of the $P_{out}O_2$ from 100 to 600 determines an increase of VO_2ML of 15 ml O₂ per liter of blood flow; at high blood flows (i.e., 4 l/min) this may account for 20–30 % of the total body oxygen consumption. Even if the oxygenation performance of modern MLs is already satisfying, a modest decrease in gas exchange efficiency is commonly seen after some days of use; any further development in membrane coating might allow to maintain the initial performance over days.

$C_{IN}O_2$: A characteristic problem of venovenous ECMO (VV ECMO) systems is recirculation, which is defined as the fraction of the oxygenated blood flow that reenters the drainage line of the circuit. A high recirculation fraction usually manifests with a high $C_{IN}O_2$; as it is shown in the formula above, any increase in $C_{IN}O_2$ may significantly impair the VO_2ML . For example, a recirculation fraction of 50 %, by reducing the difference $C_{OUT}O_2 - C_{IN}O_2$, will approximately halve the VO_2ML , functionally wasting half of the blood flow of our ECMO system. The main parameters that may affect recirculation are the position of the cannulae, their shape and features, the ratio BF/cardiac output, and the vena cava diameter.

The recirculation fraction during VV ECMO has always been difficult to quantify; methods based on oxygen as a tracer have proved to be unreliable as they are based on the rough assumption that, in the absence of recirculation, the oxygen content of the venous blood in the drainage cannula equals the theoretical mixed venous content of O₂. Most of the experience for the calculation of recirculation comes from nephrology where, in the early 1990s, besides the classical two-/three-needle methods based on blood urea nitrogen dilution, new techniques based on saline bolus dilution were introduced [2, 3]. These techniques proved to be reliable and were successfully applied to the VV ECMO [4–6], but they have not been largely introduced in clinical practice yet.

In the early 1990s, polypropylene membrane lungs (PPML) replaced the old silicon rubber membrane lungs (SRML) because of their lower resistance to blood flow, easier priming with low volumes, and higher efficiency in gas exchange. However, when PPML were used for more than 6 h, plasma leakage occurred. The technological development led to new polymethylpentene (PMP) membrane lungs [7], which maintained the superior performance compared to SRML [8] without the plasma leakage problem.

Moreover, the development of heparin-coated ECMO circuit surfaces allowed to reduce the need of anticoagulants and to avoid most of the systemic hypercoagulability secondary to the activation of the clotting cascade. The possibility of performing short-term ECMO treatments without anticoagulants extended the use of this technique to the trauma patient with acute cardiorespiratory compromise. Recently new ultra-compact ECMO systems have been developed [9]; these systems, besides improved portability, represented a significant safety improvement as they feature continuous monitoring of arterial and venous line pressure, blood temperature, hemoglobin, and saturation of the blood entering the venous limb of the circuit, useful to quickly detect high recirculation fractions during cannulae positioning.

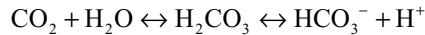
40.2 Extracorporeal CO₂ Removal and Future Perspectives

Almost all ARDS patient require hyperventilation [10] because the severe hypoxia is most frequently accompanied by an inefficient CO₂ removal. A minute ventilation (VE) as high as 15 l/min is commonly employed, and since the functional residual capacity (FRC) estimated for these patients is around 0.5–0.7 l [11], the ratio between VE and end FRC is higher than 30, whereas in a healthy man (FRC 2.5 l, VE 7 l/min) such ratio is lower than 3. This elevated mechanical ventilation need is due to the increased dead space of ARDS patients, proving that ARDS is also a microvascular disease: pulmonary pressures indeed are often increased and the development of right heart failure is common. Dead space is so significant that it is probably the strongest predictor of mortality [12] in ARDS.

High mechanical ventilation means also higher chance to induce ventilation-induced lung injury (VILI); despite the proven efficacy in terms of patient outcome

of a reduction of the tidal volume (TV) from 12 to 6 ml/kg [10], Terragni et al. recently demonstrated that also a 6 ml/kg TV can induce severe lung hyperdistension [13]. A further reduction in TV, without a concomitant rise in CO₂, can be achieved by means of extracorporeal CO₂ removal technology [14]. As explained in the introductory paragraph, CO₂ removal can be performed with blood flows far lower than the ones used for supporting oxygenation. Since lower blood flow also means smaller cannulae, hence lower invasiveness, today several extracorporeal CO₂ removal (ECCO₂R) systems are available and many efforts are made to achieve a substantial CO₂ removal from an extracorporeal blood flow close to the one commonly employed during continuous venovenous hemofiltration (CVVH) [14–17]. However, despite major improvements in extracorporeal technology, moderate/high extracorporeal blood flow rates (500–1,000 ml/min) [11, 12] are still required to remove a significant fraction (e.g., 50 %) of the total CO₂ production of an adult patient. This implies the use of large caliber vascular catheters and specific technical expertise and equipment that limits the widespread diffusion of this technique. An ideal ECCO₂R system should remove about 50 % of the total CO₂ production of an adult patient from a blood flow of 200–250 ml/min, achievable with standard double-lumen dialysis catheters; this target can only be attained by drawing from the considerable fraction of CO₂ present under the form of bicarbonate ions.

The CO₂ transfer in the ML is driven by the transmembrane delta pressure of CO₂, which is related to the dissolved CO₂: only a minor portion (about 5 %) of the blood total CO₂ content. The majority of CO₂ (~90 %) is under the form of bicarbonate ions, which are in equilibrium with the dissolved fraction as follows:



The extracorporeal CO₂ removal has been attempted with two different strategies [18]: the first is through hemodialysis, which removes CO₂ both as dissolved CO₂ and as bicarbonate ions; the other is through ventilation of blood, which removes CO₂ in gas form. The first solution requires a hemofilter and implies the replacement of the removed bicarbonate with other anions (acetate, hydroxide, THAM) to prevent electrolyte and metabolic imbalance; the latter requires only a membrane lung. Both these strategies can be enhanced by shifting the equilibrium between the CO₂ forms: alkalization increases the bicarbonate form and may enhance hemofiltration of HCO₃⁻; acidification increases the gaseous form and may enhance the ML performance. In the past both these strategies have been attempted [19–23] as short-term treatment in animal models and proved to be effective in increasing the CO₂ removal, but none proved to be safe; hence, for more than 20 years, these strategies have been locked in a drawer. In the recent times, with new technologies, these enhanced CO₂ removal techniques have been rediscovered and showed a great potential as a tool to improve extracorporeal CO₂ removal.

Cressoni et al. [24] achieved a 50 % reduction of mechanical ventilation through blood ultrafiltration. A consistent fraction of blood ultrafiltrate was removed; at the same time the lost fluid was replaced by a solution containing no bicarbonate. By this arrangement, the hemofilter removes Na⁺HCO₃⁻, whereas Na⁺OH⁻ is reinfused with the replacement solution; the net balance is the CO₂ removal. Zanella et al. [25]

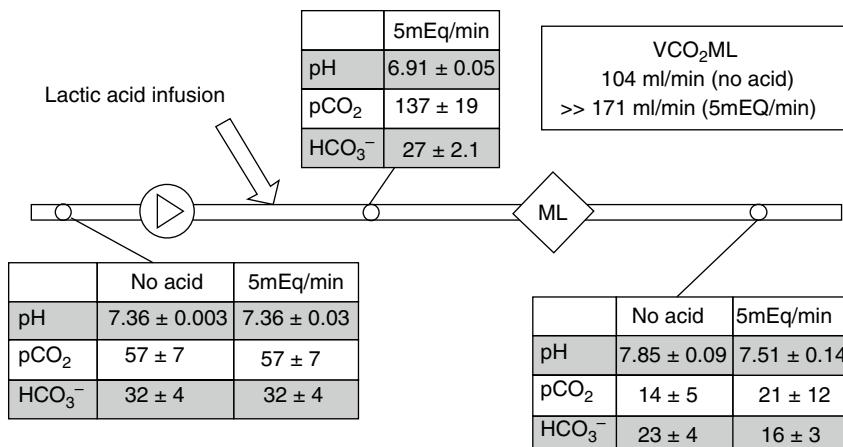


Fig. 40.1 Blood gas parameters and CO₂ removal in the extracorporeal circuit (BF 500 ml/min, GF 10 l/min) with and without acidification (5 mEq/min of L-lactic acid) [25]

Showed that acidification with a concentrated lactic acid solution may determine a substantial increase of the extracorporeal CO₂ removal of the membrane lung (VCO₂ML). In a low-flow extracorporeal system (500 ml/min), the infusion of lactic acid at 1–2–5 mEq/min increased the VCO₂ML by 16, 30, and 64 %, respectively. At the highest rate of acidification, the VCO₂ML reached 171 ml/min, a value close to the total CO₂ production of an adult man. An example of blood gas parameters in the extracorporeal circuit during acidification is shown in Fig. 40.1. Preliminary data [26] in the animal model showed that a 48-h infusion of 2.5 mEq of lactic acid in a low-flow ECCO₂R system (BF 250 ml/min) was safe and efficient in determining a stable increase (60–80 %) of VCO₂ML compared to the same setting without acid infusion. Since lactate is a metabolizable compound and a source of calories, to avoid overfeeding and a consequent increase in total CO₂ production, the calories infused as lactate should be considered in the daily total calorie intake. Anyway during lactic acid infusion, when the total caloric input was maintained constant, the resulting increase of total VCO₂ was negligible [27]. Promising results have also been achieved with a system based on ventilation of acidified dialysate [28]. In this series of experiments, no complication ascribable to lactic acid infusion was reported.

Future development may imply the use of other metabolizable acid such as citric acid, which may play a dual role of blood acidification and regional anticoagulation. Another option may be the use of non-metabolizable acid (e.g., hydrochloric acid), which however requires more complex dialysis system to remove the strong anions and to prevent the resulting progressive metabolic acidosis.

Recently new ECCO₂R systems have been developed [29]; new features include an integrated gas exchange membrane and centrifugal blood pump and the possibility to continuously monitor the VCO₂ML. These systems however extract only 50–100 ml of carbon dioxide per minute from a blood flow of 350–500 ml/min. The development of ultra low-flow-enhanced ECCO₂R systems may allow a widespread

diffusion of this technique, further reducing invasiveness and allowing its application even outside the intensive care unit setting [30].

40.3 Clinical Management Challenges

40.3.1 ECMO for Refractory Cardiac Arrest (RCA)

ECLS represents a valuable tool for the support of cardiac and respiratory functions. Obviously this is true only when top-level standard care is provided together with the extracorporeal support.

In particular, standardized protocols of care should be implemented in patients suffering from RCA:

- Optimal standard ALS care should be guaranteed and constitutes the conditio sine qua non for the institution of ECLS. Of utmost importance is the adequacy of chest compressions, with the minimization of interruptions from the moment of collapse to the start of extracorporeal support. The use of mechanical chest compression devices seems a promising option to achieve this objective (1).
- Strict protocols should indicate the inclusion and exclusion criteria, leaving to the attending clinician the possibility to deviate in specific circumstances on a case-by-case basis. In particular, out-of-hospital RCA victims show a far worst prognosis when compared to in-hospital RCA patients (2). Accurate criteria are fundamental to avoid futile implantations.
- No-flow time (i.e., the time from collapse to the beginning of CPR) is a fundamental determinant of neurologic outcome. Low-flow time (from the beginning of CPR to ROSC or ECLS start) is also relevant and should be kept to a minimum (ideally below 45'). Strategies should be implemented to pursue this objective. Implantation in places of the hospital other than theaters and ICUs is common, while only few reports have been published on the out-of-hospital implantation and at the moment this seems, in our opinion, not advisable for several clinical and organizational reasons. An exception could be represented by mass events where a cardiac event is likely (e.g., marathons), where an ECMO-capable advanced medical facility might be implemented.
- Neurologic damage represents a frequent cause of morbidity and mortality in this setting. Secondary ischemic insults represent an important cause of permanent neurologic damage. It is hence fundamental to standardize care (therapeutic hypothermia, seizures management, sedation, etc.) and neurologic monitoring (clinical, radiological, EEG, somatosensory evoked potentials, as discussed in the specific chapter in this book).
- Additional predictors of neurologic outcome should be sought and investigated in order to minimize futile assistances and give proper indications for sustaining support.
- Early coronary angiography should be performed in all patients with an ischemic ECG post-ROSC and in patients with a possible cardiac cause of RCA when no other cause is evident. It should be considered and weighed against possible

contraindications in all patients with an apparently normal ECG post-ROSC, as several studies revealed a considerable amount of patients demonstrating occluded coronary arteries despite a silent post-ROSC ECG.

40.3.2 Ischemia/Reperfusion Injury

Reperfusion injury represents an important cause of morbidity, particularly in cardiogenic shock and RCA patients. Endothelial and mitochondrial damage can result into a systemic inflammatory response leading to profound distributive shock. Apart from optimizing pre-ECMO perfusion as possible, many strategies have been investigated to minimize such damage, but none, apart from therapeutic hypothermia, is now in clinical practice.

The administration of NO donors constitutes a promising strategy to minimize ischemia/reperfusion injury in many organs and is under investigation in different settings (Shock 2013).

Centrifugal ECMO pumps provide a continuous flow pattern. Arterial pulsatility is hence lost when native cardiac output is dramatically reduced. Pulsatile flow showed a protective effect on endothelial function and inflammation in several studies. Various strategies are commonly implemented to maintain a certain degree of pulsatility (see Chap. 9 for further details), but their impact on outcome has still to be determined.

40.3.3 Evaluation and Reconditioning of Organs for Transplant

Brain-dead ECMO patients (HBD, heart-beating donors) frequently become organ donors, and in these patients the extracorporeal support guarantees adequate organ perfusion until the harvesting of organs.

In recent years two additional techniques have been realized for organ procurement. Abdominal organs from non-heart-beating donors (NHBD) can be perfused with femoro-femoral VA ECMO after death has been declared; an endo-vascular clamp is inflated in the descending thoracic aorta to avoid brain and heart perfusion. The second promising technique is represented by ex vivo lung perfusion; marginal lungs are extracted from the donor and reconditioned for a few hours with an ECMO machine (see the specific chapter for details) and subsequently implanted in the recipient if they match implantation criteria. Both techniques are described in the specific section of this book and represent a potentially relevant resource for organ procurement.

40.4 Organizational Challenges

ECMO represents a typical low-volume, high-risk technique. Organizational aspects are hence of paramount importance to minimize complications and optimize management, in order to ultimately improve patients' outcome.

A number of issues still need to be improved in this regard:

- Referral to high-volume centers has been shown to improve outcome. The implementation of hub-and-spoke models is essential for both VV and VA ECMO. Standardized protocols for referrals to the ECMO center are critical, and so is the development of retrieval programs. Every established ECMO center should perform at least 10–15 runs per year in order to maintain an adequate performance and should provide retrieval service for regional spokes.
- ECMO-related complications markedly affect patients' outcome. These should be accurately recorded, and a systematic appraisal carried out. Regular debriefings should be carried out with all the team to critically examine every ECMO run. Periodic review of practice and protocols is dictated on the basis of audit results.
- Due to the number and extent of complications, ECMO cannulation and management should always be provided from the most experienced staff. This on the other hand constitutes a limit to the training of new staff. "On-the-field training" represents nowadays the standard in most centers. Simulation techniques are being developed in several institutions and may represent the future of ECMO education. They could also become an invaluable tool for continuous training and refresh and for the revision of critical incidents.

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